Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Pulmonary artery targeted therapy in treatment of COVID-19 related ARDS. Literature review

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ABSTRACT

Introduction: The most grievous complication of the COVID-19 is the acute respiratory distress syndrome. A specific, rescue treatment for rapidly deteriorating patients should emerge to improve respiratory function and help patients to survive the most challenging period. Drugs used in targeted therapy of pulmonary arterial hypertension (PAH) appears to be suitable for this task and this article describes their potential for treatment of severe cases of COVID-19.

Methods: The authors reviewed the following databases for randomized controlled trials, reviews and meta-analyses published up to July 2020: Pubmed, Scopus, Google Scholar, Cochrane Database and ClinicalKey. The authors included every study contributory to the assessment of the potential of drugs used in targeted PAH therapy in treatment of COVID-19.

Results: Endothelin receptor antagonists, phosphodiesterase 5 inhibitors, riociguat and prostacyclin have proven ani-inflammatory effect and reduce pulmonary artery blood pressure, lung oedema and remodelling. Bosentan shows antiviral properties and sildenafil, as well as epoprostenol, inhibits apoptosis of lung epithelial cells. Among patients with lung lesions the decrease of pulmonary blood pressure can lead to increase of ventilation/perfusion mismatch and decrease of blood oxygenation.

Conclusions: Among all assessed drugs bosentan, sildenafil and epoprostenol appear to be most promising and a combination of these drugs should be considered due to synergism. The targeted PAH therapy in treatment of COVID-19 associated ARDS could be a useful tool saving lives of patients with severe SARS-CoV-2 infection, however, its introduction should be investigated and monitored very carefully as it can lead to transient deterioration of patient condition.

1. Introduction

The COVID-19 epidemy broke out in December 2019 in Wuhan, China, and within a couple of months SARS-CoV-2 spread all around the world, which made it the greatest pandemic that human kind has experienced for decades [1,2]. According to WHO October 27, 2021, there were 243,857,028 confirmed cases of COVID-19 and 4 953,246 deaths in course of this disease worldwide [1]. Hu et al. in their metanalysis indicated that 12.6–23.5% of SARS-CoV-2 infections are severe and mortality of COVID-19 ranges from 2% up to 4.4% [2]. The most grievous COVID-19 complication is the acute respiratory distress syndrome, which afflicts 9% to even 31% of SARS-CoV-2 infected patients and respiratory failure is the main cause of death among COVID-19 patients [2,4]. Regarding the gravity of this problem, physicians and scientist all over the world put a great effort in investigation of this disease and development of efficient treatment strategies, especially for patients with acute respiratory distress syndrome (ARDS).

Despite many clinical studies involving thousands patients optimal COVID-19 therapy remains controversial. While oxygen therapy is still a cornerstone of management of severe cases of this disease, different

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complementary therapies were proposed in order to reduce mortality rates. Patrucco et al. made throughout analysis of studies regarding COVID-19 treatment. Metanalyses demonstrated that corticosteroids are beneficial for patients who needed oxygen support, with or without mechanical ventilation, significantly reducing mortality rates [5]. However, corticosteroids had no effect on patients who did not needed oxygen support [5]. Clinical trials demonstrated that antiviral agents had no effect on COVID-19 patients except remdesivir, which reduce time to recovery from severe COVID-19 but do not reduce mortality rates [5]. In case of other anti-inflammatory agents such as anti-interleukin-6 drugs there are mixed results and their efficacy still needs to be proven [5]. Therefore, among drugs used commonly in treatment of COVID-19 only corticosteroids reduce mortality rates.

Regarding problems of COVID-19 treatment there is another important factor. Analysis by Li and Ma shows that among these patients the clinical symptoms are most often inconsistent with the severity of laboratory and imaging findings and they may deteriorate rapidly [4]. Therefore, a specific, rescue treatment for rapidly deteriorating patients should emerge in order to stop further worsening of their condition, improve respiratory function and help patients to survive the most challenging period of the disease. Drugs used in targeted therapy of pulmonary arterial hypertension appears to be suitable for this task and this article describes their potential for treatment of severe cases of COVID-19, with most important studies gathered in Table 1.

2. Materials and methods

2.1. Literature search strategy and study selection

Between January 2020 and July 2020 the following electronic databases were reviewed: Pubmed, Scopus, Google Scholar, Cochrane Database and ClinicalKey. The search included: clinical trials with human subjects, original studies with rat or mouse models, original studies on cell lines, metanalyses, systematic reviews and reviews, all in English.

2.2. Inclusion and exclusion criteria

The inclusion criteria for the study were defined with use of population–intervention–comparison–outcome (PICO) formula. Abstracts were considered if the following inclusion criteria were fulfilled..

2.2.1. Population

Patients with ARDS, patients treated with pulmonary artery targeted therapy, patients with viral infection i.e. COVID-19, patients form regions with increased risk of SARS-CoV-2 infection, reliable rat or mouse models, cell line studies.

2.2.2. Intervention

Use of pulmonary artery targeted therapy agents.

2.2.3. **Comparison**

Comparison of pulmonary artery targeted therapy to placebo or conventional therapy, comparison of different drugs, comparison of conventional therapy to conventional therapy with pulmonary artery targeted therapy.

2.2.4. Outcome

Reduction of viral infection morbidity, severity, mortality and time to recovery; reduction of cytopathogenicity and virion multiplication considering in vitro studies.

2.2.5. Study design

Clinical, animal or in vitro studies investigating efficiency of pulmonary artery targeted therapy in treatment COVID-19-associated ARDS. Metanalyses and reviews summarizing such trials.

Table 1
Summary of selected original studies describing effects of presented drugs in ARDS treatment.

Authors (year) [reference number]	Subjects (n)	Intervention/ measured parameters	results
Guimarães et al. [15]	Mice with oleic acid induced lung injury: Sham group (8) 1% oleic acid alone – controls (8) Pretreatment with bosentan (24)	Induction of lung injury by i.v. administration of 1% oleic acid alone or 30 min after bosentan i. v. Assessment of lung vessels permeability by measurement of Evans blue concertation in lungs.	Bosentan reduces pulmonary vessel permeability and plasma transudation in dosage dependent manner.
Funke et al. [17]	Human umbilical vein endothelial cells infected with the cardiotropic coxsackie-B3 virus strain Nancy.	24 h incubation with bosentan in increasing doses. Assessment of virus replication by measurement of coxsackie-adenovirus receptor (CAR) mRNA in PCR.	Bosentan significantly reduced CAR mRNA levels in a dosage dependent manner. Cell incubation with endothelin 1 (ET-1) resulted in notable increase of CAR mRNA.
Knobloch et al. [25]	Human airway smooth muscle cells (HASMCs) stimulated with ET-1 or tumour necrosis factor α (TNF-α).	Preincubation of cell colonies with bosentan or macitentan or abrisentan. Histological assessment of HASMC proliferation and measurement of selected inflammatory markers.	All endothelin receptor antagonists (ERAs) significantly reduced HASMC proliferation in both ET-1 and TNF-α colonies. Bosentan and macitentan reduced inflammatory induced expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 6 (IL-6). Ambrisentan decreased only IL-6 expression. ERAs most likely can reduce inflammatory response in human airways and inhibit remodelling of bronchi.
Gerlach et al. [26]	Alveolar macrophages isolated from the broncho-alveolar lavage of non-smokers (11), current smokers without COPD (10), smokers with COPD (8)	Isolated macrophages were incubated with lipopolysaccharide (LPS) for 24 h. Bosentan or ambrisentan were added 1 h prior the incubation.	Both, bosentan and ambrisentan reduces release of IL-6, chemokine ligand 2 and metalloproteinase 9 by alveolar macrophages stimulated with LPS. Both ERAs most likely can reduce inflammatory response in human airways.
Imhof et al. [27]	Adult female C57BL/6 J mice with antigen-induced arthritis treated with: Bosentan (10) Ambrisentan (10) Saline - controls (10).	Intravenous administration of bosentan 100 mg/kg or ambrisentan 10 mg/kg or saline every 24 h. Analysis of pain-related behaviour and expression of	Bosentan, but not ambrisentan, significantly reduced inflammation, joint swelling and pain-related behaviour of investigated animals.

(continued on next page)

Table 1 (*continued*)

Authors (year) [reference number]	Subjects (n)	Intervention/ measured parameters	results
		inflammation marker genes.	
Kosutova et al. [41]	New Zeland white rabbits: Controls (5) Acute lung injury treated with sildenafil (5) Acute lung injury without any treatment (5)	Lung injury was induced by repetitive saline lavage. 5 individuals received 1 mg/kg of sildenafil i.v. All subject were ventilated with oxygen for 4 h and sacrificed in order to harvest lungs.	Sildenafil led to a significant reduction of lung oedema, neutrophil infiltration, epithelial lung cell apoptosis, caspase 3 levels and notably decreased inflammatory response with decline of tumour necrosis factor α (TNFα), IL-6 and IL-8.
Qiao et al. (2020) [50]	Computational analysis	Molecular dynamics simulations of various drug docking to the active site of the main SARS-CoV-2 protease - 3CL protease.	Among other drugs tadalafil and sildenafil are very likely inhibitors of 3CL protease and inhibition of 3CL protease would reduce SARS-CoV-2 replication.
Cornet et al. [51]	Patients with ARDS (10)	Single dose of 50 mg sildenafil citrate administered via a nasogastric tube.	Sildenafil significantly decreased pulmonary blood pressure but led to decrease of arterial blood oxygenation by increasing shunt fraction.
Abdelaziz et al. [53]	Healthy controls (10) Rats with induced silicosis (10) Rats with induced silicosis treated with tadalafil (10)	Induction of lung inflammation and fibrosis – silicosis. Treatment with tadalafil 1 mg/kg p.o. once daily for 8 weeks. Cytological and histological lung assessment.	Tadalafil led to significant reduction of pulmonary vessels wall thickness and extracellular matrix decomposition, as well as inhibition of inflammation in compare to silicosis group.
Guerra-Mora et al. [55]	Wistar rats: Healthy controls (8) Ischaemia-reperfusion group (8) Ischeamia-reperfusion + sildenafil group (8) Ischeamia-reperfusion + tadalafil group (8)	Icheamia-reperfusion model was performed by 8 h of pulmonary artery occlusion. Rats were treated with sildenafil 0.7 mg/kg or tadalafil 0.15 mg/kg. Assessment of oedema and measurement of pulmonary arterial pressure, pulmonary venous pressure, capillary filtration coefficient and reactive oxygen species (ROS) levels.	Tadalafil, in contrast with sildenafil, was ineffective in reduction of lung oedema. Both drugs reduced ROS formation
Chamorro et al. [57]	Human pulmonary arteries (14) Wistar rats (41)	Assessment of the impact of riociguat and sildenafil on pulmonary arteries of rats in vivo and in vitro, as well as human pulmonary arteries in vitro. Some in vitro arteries were exposed to hypoxia.	Riociguat induced more potent vasodilatation than sildenafil in vitro and in vivo, in both human and rat models. Under hypoxic conditions riociguat was approximately 3-fold more potent than under physiological oxygen levels.
Donda et al. [58]	Sprague-Dawley rats: Normoxia + placebo (6) Normoxia + riociguat (6) Hyperoxia + placebo (6) Hyperoxia + riociguat (6)	Hemodynamical and histological analysis of rat pulmonary arteries.	Riociguat significantly reduces inflammation and vascular remodelling in compare to placebo group, therefore it protects lungs in rat model of hyperoxia-induced lung injury.
Toki et al. [61]	Wilde type and prostacyclin receptor deficient mice with LPS-induced acute lung injury.	Biochemical, cytological and histological analysis of murine lungs.	Prostacyclin significantly attenuated lung infiltration by neutrophils and reduced inflammatory response by increase of IL-10 and decrease of TNF-α.

Studies were excluded for the following reasons: intervention with no pulmonary artery targeted therapy.

2.3. Outcome measures

The primary outcome measure to assess the efficacy of pulmonary artery targeted therapy in treatment of COVID-19-associated ARDS was the reduction mortality. Other measures were reduction of infection severity, decrease of virus replication, etc.

2.4. Data extraction

The following data for each study was extracted: number of subjects, population specification, animal species, cell line specification, route of drug administration, study period, type of viruses, viral strand numbers, impact on virulence and virus replication, study outcomes.

2.5. Data analysis and synthesis

To compare and summarize the studies, data was extracted and impact of pulmonary artery targeted therapy was evaluated. The methodology was critically assessed and results of animal or in vitro studies have been referred to clinical conditions. The statistical significance was defined as a p-value< 0.05.

2.6. Assessment of risk of bias

The studies were evaluated for quality and risk of bias by assessment of creditability of used scales and measurement tools and analysis of authors statements.

3. Endothelin receptor antagonists

3.1. Endothelin in Acute Respiratory Distress Syndrome

Endothelin is a vasoactive peptide composed of 21 amino acids, which appears in three isoforms of which ET-1 (endothelin type 1) is most widely expressed, and thus, most studied [6]. ET-1 is a potent vasoconstrictor produced exclusively by early passage endothelial cells

[6]. In lungs two types of endothelin receptors are expressed, which are type A (ET_A) and type B (ET_B) [6]. The first one is expressed by vascular smooth muscle cells and mediates vasoconstriction. The other receptor occurs in two subtypes, ET_{B1} and ET_{B2} and the first one is expressed by endothelial cells and mediates endothelium-dependent vasorelaxation, while the second one is expressed by vascular smooth muscle cells and mediates vasoconstriction [6]. Although this data implicates that ET-1 can induce both vasodilatation and vasoconstriction, in lungs approximately 90% of endothelin receptors are ET_A, therefore vasoconstriction of pulmonary arteries is the most pronounced effect of ET-1 [6]. Chen et al. show that hypoxia induces increased expression of ET1, ET_A and ET_B in lungs and respiratory system vessels [3]. Moreover, ET_A activation leads not only to acute vasoconstriction but also vascular remodelling through smooth muscle proliferation, which processes are crucial for pulmonary hypertension development [3,7,8]. Furthermore, Druml et al. reported significantly elevated plasma levels of ET-1 among patients with acute respiratory distress syndrome comparing to healthy individuals, indicating increased production and decreased degradation of endothelin in course of ARDS [9]. Furthermore, Li et al. show that endothelin upregulates the expression of high mobility group box 1 (HMGB1) in human bronchial epithelial cells and HMGB1 is a well-known activator of nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing type 3 (NLRP3) inflammasome, which mediates inflammation and cell pyroptosis [6]. Moreover, NLRP3 mediated macrophage pyroptosis was reported to be the key element of acute lung injury and ARDS [7]. Interestingly, it appear that the ET-1 induced expression of HMGB1 is mediated through ET_A but not ET_B [6]. The role of ET-1 and NLRP3 in development of ARDS is summarized in Fig. 1.

Regarding SARS-CoV-2 it is important to mention that this virus penetrates into lung cells through association with angiotensin converting enzyme 2 (ACE2), which is expressed by pneumocytes, leading

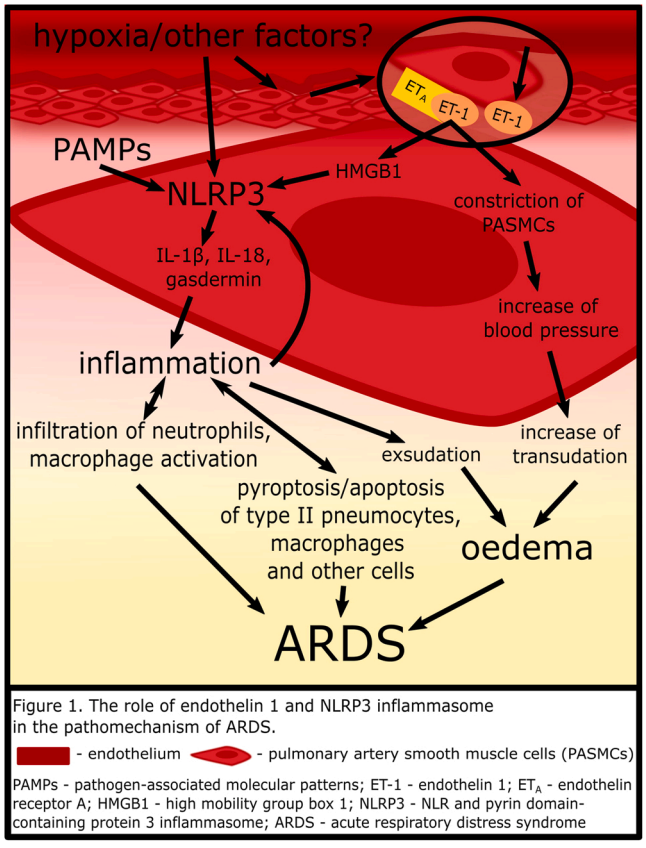

Fig. 1. The role of endothelin 1 and NLRP3 inflammasome in the pathomechanism of ARDS.

to decrease in its level [8]. ACE2 converts angiotensin II, which leads to blood pressure increase, into angiotensin (1−7), which leads to vasodilatation inter alia due to attenuation of ET-1 effects, therefore coronavirus associated ACE2 depletion leads to pulmonary hypertension [8]. Moreover, SARS-CoV-2 causes viral pneumonia, which may lead to ARDS in 15.6–30% of cases [4]. Considering a prominent role of ET-1 in PAH and ARDS Badagiacca et al., as well as Javor and Salsano hypothesized that endothelin receptor antagonists could be helpful in treatment of SARS-CoV-2 induced lung injury and following sections are the analysis of available studies regarding endothelin receptor inhibitors in view of COVID-19 [10,11].

3.2. Bosentan

Bosentan is the first endothelin receptor antagonist (ERA) registered as a treatment for pulmonary hypertension [12]. It is an antagonist of both ET_A and ET_B, however, its affinity to ET_A is approximately 100 times greater than for the ET_B [6]. Bosentan is proven to reduce pulmonary arterial pressure and arterial vessels resistance, increase cardiac output and improve performance of patients with PAH [13,14]. Moreover, it has been reported that bosentan is effective in treatment of ARDS [15,16]. Guimarães et al. show that bosentan reduces pulmonary vessel permeability and plasma transudation in dosage dependant manner in murine, oleic acid induced ARDS model [15]. Furthermore, Araz indicated that bosentan reduces inflammation and free radicals levels and is as effective as dexamethasone in ARDS treatment [16]. Interestingly, Funke et al. show that bosentan has also antiviral properties [17]. Researchers infected human umbilical vein endothelial cells with the cardiotropic coxsackie-B3 virus strain Nancy. The virus replication level was assessed by coxsackie-adenovirus receptor (CAR) mRNA expression quantified by RT-PCR [17]. Bosentan significantly reduced CAR mRNA levels in a dosage dependent manner. Furthermore, cell incubation with ET-1 resulted in notable increase of CAR mRNA in examined specimens [17]. Curiously, ET_A knock-out cells showed no significant difference in CAR expression and drug effect compared to unmodified cells, however, ET_B knock-out cells showed approximately 30% reduction of CAR mRNA and abolition of bosentan effect. These results prompted Funke et al. to conclusions that ET-1 through ET_B increases CAR expression and that bosentan can protect endothelial cells from adenoviral and enteroviral infection [17]. This study has proven that endothelin through ET_B can alterate the expression of certain receptors, therefore it can be assumed that ET-1 could have an impact on other endothelial receptors i.e. ACE1 or ACE2. In fact, Kiowski et. reported a significant reduction of plasma angiotensin II levels among patients with chronic heart failure treated with bosentan in total dosage of 300 mg [18]. This could be an effect of bosentan inducing decrease of ACE1 expression or increase of ACE2 expression, however, there is no scientific data delineating the mechanism of ERA induced ang II concentration decline. Nevertheless, this effect of bosentan could be very helpful in COVID-19 treatment, as it was described that SARS-CoV-2 infection is associated with significant increase of ang II plasma levels and this hormone increases a severity of ARDS [19,20]. Furthermore, Nally et al. demonstrated that ang II markedly enhanced ET-1 induced contraction of bovine bronchial smooth muscles and this effect was mediated by type 1 ang II receptor [21]. Considering that SARS-CoV-2 leads to an increase of ang II concentrations and can lead to hypoxemia, which is a prominent inductor of ET-1 production, the interplay between these two mediators and the enhancement of their activity could play a major role in the SARS-CoV-2 induced ARDS [7,19]. Therefore, bosentan by both reducing ang II levels and ET-1 antagonism could reduce lung injury, pulmonary transudation and improve condition of patients with severe COVID-19 [12,15,18]. In fact, Guo et al. presented a case of bosentan use as a rescue treatment for patients with ARDS in course of H7N9 virus infection [22]. Researchers obtained significant reduction of the right ventricular blood pressure, notable increase of Horowitz Index and improvement of patient condition, what led them to the conclusion that bosentan could be used in

treatment of severe cases of viral acute respiratory distress syndrome [22]. Its potential role in ARDS treatment is delineated in Fig. 2.

Considering all above, bosentan could be effective in treatment of COVID-19 associated ARDS by reduction of inflammation, free radicals concentration and angiotensin II levels, decrease of pulmonary blood pressure and pulmonary vessel permeability, thus decrease of pulmonary transudation and finally inhibition of the virus proliferation. However, this hypothesis needs a confirmation in clinical and laboratory studies.

3.3. Other Endothelin receptor antagonists

There are two more endothelin receptor antagonists used in treatment of pulmonary hypertension, which are ambrisentan, a selective ETA antagonist and macitentan, a nonselective ETA/ETB antagonist [23,24]. Although these drugs are effective in treatment of PH, there are no studies investigating their impact in treatment of ARDS. Thor et al. investigated 112 patients with PAH treated with either bosentan or macitentan and discovered no significant difference in therapy outcome and two-year survival rate [23]. Bedan et al. indicated that macitentan has a similar mechanism of action as bosentan, however, it has a longer duration of action and exhibits higher antagonistic potency than bosentan and ambrisentan in pulmonary smooth muscle cells [24]. Considering that both bosentan and macitentan are nonselective ERAs it can be assumed that these drugs will have a similar impact not only on patients with PH, as it was demonstrated by Thor et al., but also on patients with ARDS [23,24]. However, this hypothesis needs a clinical confirmation.

Knobloch et al. investigated the impact of all three ERAs on inflammation induced pulmonary smooth muscle cell proliferation [25]. Researchers revealed that bosentan and macitentan reduced inflammatory induced expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 6 (IL-6) but ambrisentan decreased only IL-6 expression [25]. However, there was no significant difference in ERAs inhibition of cell proliferation. Another study by Gerlach et al. show that bosentan and ambrisentan reduces release of IL-6, chemokine ligand 2 and metalloproteinase 9 by alveolar macrophages stimulated by lipopolysaccharide [26]. However, Imhof et al. show that ambrisentan, in contrast to bosentan, was unable to reduce inflammation and pain-related behaviour of animals in murine antigen-induced arthritis model [27]. Furthermore, in previously described study conducted by Funke et al. ambrisentan showed no antiviral properties but bosentan reduced virus proliferation [17]. These researches indicate that ET-1/ETB axis is important in inflammation and receptor expression mediation, therefore abrisentan, as a selective ETA antagonist appears to be the least suited as a potential treatment of COVID-19 associated ARDS. Macitentan would possibly have comparable impact on COVID-19 associated ARDS as bosentan due to similar mechanism of action of these two drugs. Their potential role in ARDS treatment is delineated in Fig. 2.

In summary of this group of drugs, it can be stated that bosentan is the most studied and considering the current state of knowledge, the most promising potential treatment of COVID-19 associated ARDS, while ambrisentan appears to be least suited for that purpose. However, the usefulness of all the ERAs in treatment of severe cases of SARS-CoV-2 infection needs to be investigated in clinical studies.

4. Phosphodiesterase 5 inhibitors

4.1. Phosphodiesterase 5 in ARDS

Nitric oxide (NO) is one of the most important vasodilators in human body. According to Dou et al. NO stimulates the soluble guanylyl cyclase to produce the cyclic guanosine monophosphate (cGMP), which in turn activates the cGMP-dependent protein kinase (PKG) [28]. PKG leads to the vascular smooth muscle dilatation through reduction of the intracellular Ca^{2+} concentrations and inhibition of myosin light chain phosphatase, thus desensitization of myofilaments to Ca^{2+} [28]. Considering that vasoconstriction is the key element of PAH pathomechanism, increased cGMP plasma levels, therefore vasodilatation, would be beneficial for patients [29]. Degradation of cGMP is catalysed by phosphodiesterase (PDE), e.g. PDE-5, therefore scientists hypothesized that inhibition of PDE-5 would decrease pulmonary arteries blood pressure and improve patient's outcome. Lan et al. analysed 21

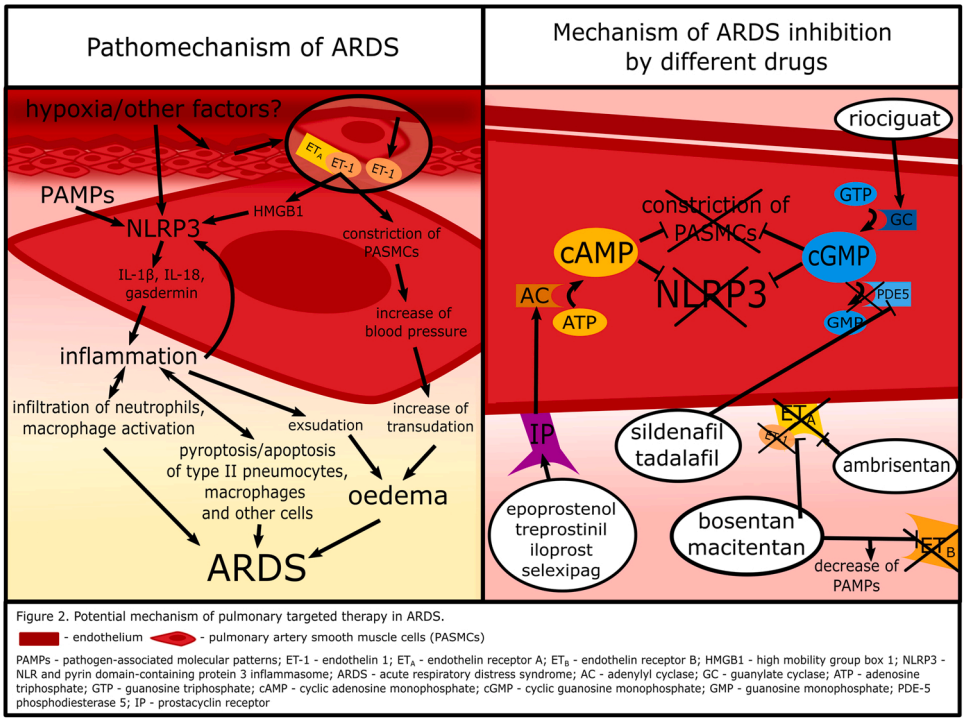

Figure 2. Potential mechanism of pulmonary targeted therapy in ARDS.

- endothelium - pulmonary artery smooth muscle cells (PASMCs)

PAMPs - pathogen-associated molecular patterns; ET-1 - endothelin 1; ET_A - endothelin receptor A; ET_B - endothelin receptor B; HMGB1 - high mobility group box 1; NLRP3 - NLR and pyrin domain-containing protein 3 inflammasome; ARDS - acute respiratory distress syndrome; AC - adenylyl cyclase; GC - guanylate cyclase; ATP - adenosine triphosphate; GTP - guanosine triphosphate; cAMP - cyclic adenosine monophosphate; cGMP - cyclic guanosine monophosphate; GMP - guanosine monophosphate; PDE-5 phosphodiesterase 5; IP - prostacyclin receptor

Fig. 2. Pulmonary artery targeted therapy in ARDS.

randomized clinical trials regarding PAH and concluded that PDE-5 inhibitors, sildenafil and tadalafil, significantly decrease symptom intensity and improve performance and comfort of patients with PAH [29]. Considering such a beneficial effect in PAH scientists investigated the impact of PDE inhibitors on ARDS [30–35]. Roland et al. reported that in rat model of ischemia-reperfusion lung injury selective and non-selective PDE inhibitors were able to improve lung compliance and perfusion [30]. However, among all inhibitors, theophylline provided the best protection of lung function [30]. The reason is probably the greater importance of cGMP-mediated pathways than cAMP-mediated pathways in lung protection [31]. However researchers showed that both cAMP and cGMP decrease inflammation through inhibition of NLRP3 inflammasome, thus possibly can limit lung injury in ARDS [36, 37]. In sheep ARDS model Rovira et al. reported that NO inhalation led to increase of cardiac output, lung ventilation and lung perfusion in comparison to control group [32]. Nitric oxide inhalation also resulted in 80% increase in plasma cGMP levels, therefore researchers concluded that the protective effect of NO in lung injury is mediated by cGMP [32]. Bopp et al. in rat LPS-induced lung injury model investigated impact of PDE-sensitive and PDE-stable cGMP on lung condition [33]. Both cGMPs significantly decreased pulmonary artery blood pressure, however, the effect of PDE-sensitive cGMP was lower and notably deteriorated within two hours after administration [33]. These studies indicate that cGMP acts as a protector in ischemia-reperfusion and endotoxin-induced lung injury/ARDS. Therefore, PDE-5 inhibition can protect lungs through increase of cGMP plasma concentration, thus reduction of pulmonary blood pressure and vascular leakage [34,35]. Interestingly, human neutrophils preincubated for 10 min with the NO donor 3-morpholi-nosydnonimine hydrochloride (SIN-1) and primed with platelet activated factor showed significant reduction of elastase release [38]. This effect was positively corelated with SIN1 dosage and abolished by its inhibitor. Furthermore, Fülle et al. reported that preincubation of human monocytes with SIN1 significantly reduced IL-1β release after their activation with LPS [39]. Therefore, it is possible that cGMP inhibits activation of NLRP3 inflammasome and inflammatory response in lungs.

Considering aforementioned studies PDE-5 inhibitors through the elevation of cGMP levels protects lungs and respiratory function not only by reduction of pulmonary arteries constriction and vascular leakage but also by inhibition of inflammation and restriction of lung tissue injury by elastase. The following sections describe a potential use of these properties in treatment of SARS-CoV-2 infections.

4.2. Sildenafil

Sildenafil is a selective PDE-5 inhibitor and, as such, elevates cGMP plasma concentrations and leads to vasodilatation, therefore it is frequently used in treatment of PAH [40]. As it was described above cGMP has a protective effect on lungs, therefore, many scientists considered the administration of sildenafil to patients with ARDS as a reasonable therapeutic option. Kosutova et al. investigated the impact of sildenafil on lungs in rabbit ARDS model [41]. This PDE-5 antagonist in dosage of 1 mg/kg b.w. led to a significant reduction of lung oedema, neutrophil infiltration, epithelial lung cell apoptosis, caspase 3 levels and notably decreased inflammatory response with decline of tumour necrosis factor α (TNFα), IL-6 and IL-8 [41]. These results are consistent with previously described findings and with many more, indicating that sildenafil reduces superoxide formation in lungs, significantly decreases inflammation and reduces lung injury in ARDS models (Fig. 2) [30,31, 42–47]. Due to these properties of sildenafil Horowitz and Freeman and Sansone et al. hypothesized that this drug could be helpful in inhibition of inflammation and improvement of respiratory function of patients with SARS-CoV-2 infection [48,49]. Quiao et al. performed a computational analysis of potential inhibitors of SARS-CoV-2 spike protein and 3 C-like protease [50]. The first protein is crucial for virus penetration into the host cell, as it connects with ACE2, while the second is an enzyme crucial for SARS-CoV-2 protein cleavage, thus new virion formation. The virtual simulation revealed that sildenafil can possibly have a notable affinity to 3 C-like protease, therefore by its inhibition sildenafil may be able to reduce the virus replication [50]. Although many studies show sildenafil as a potential effective drug in treatment and prevention of lung injury in course of COVID-19, not all are as promising. Cornet et al. investigated the impact of a single dose of 50 mg sildenafil citrate administered via a nasogastric tube on respirate function of patients with ARDS [51]. Although sildenafil significantly decreased pulmonary blood pressure, it did not improved blood oxygenation. Quite opposite, 50 mg of sildenafil resulted in transient increase of shunt fraction and decrease of arterial blood oxygenation, therefore researchers concluded that this drug is not appropriate for ARDS treatment [51]. This study stays in contrast with previous ones, however this may be an effect of the fact that in animal models sildenafil was administered right after the induction of lung injury, thereby could prevent inflammation and transudation. However, in clinical study performed by Cornet et al. patients had advanced changes in lungs including oedema and observation was only 6 h long, therefore there could be simply not enough time to observe a decrease of inflammation and oedema and inhibition of injury progress in comparison to control group. Furthermore, lung injury resulting from epithelium apoptosis and matrix destruction, which most likely occurred in these cases, cannot be fixed in couple of hours, thus long-term results could be more informative. Nonetheless, this research indicate that sildenafil is probably not well suited for emergency treatment of patients with advanced lesions. However, to confirm the potential role of sildenafil in COVID-19 as an anti-inflammatory, antiviral and antioedematous agent, a clinical study is needed and Isidori et al. opened the DEDALO project, which is a multicentre clinical trial with aim to evaluate the improvement of patients with moderate-severe and severe COVID-19 [52]. Hopefully, this important research will allow to reliably assess the usefulness of sildenafil in treatment of SARS-CoV-2 infections.

4.3. Tadalafil

Tadalafil is another selective PDE-5 inhibitor successfully used in treatment of pulmonary hypertension [29]. Considering that it has the identical mechanism of action as sildenafil its impact on patients with ARDS was expected to be corresponding to that of the other drug. In fact, Abdelaziz et al. reported tadalafil in dose of 1 mg/kg b.w. led to significant reduction of pulmonary vessels wall thickness and extracellular matrix decomposition, as well as inhibition of inflammation in rat silicosis model [53]. Another research confirmed anti-inflammatory effect of tadalafil in rat model of prostatitis [54]. However, Guerra-Mora et al. reported that in rat ischaemia-reperfusion lung injury model tadalafil, in contrast with sildenafil, was ineffective in reduction of lung oedema [55]. Moreover, although tadalafil was administered in two times higher dosage than sildenafil, the latter more potently reduced oxidation stress and inflammatory response in injured lungs [55].

This leads to conclusion that, in spite of the fact that in computational analysis by Quiao et al. tadalafil shows similar to sildenafil affinity to SARS-CoV-2 3 C-like protease and reduction of pulmonary blood pressure, it appears to be less suited for treatment of COVID-19 than sildenafil due to lower reduction of inflammation and probably lack of antioedematous properties [50].

5. Riociguat

Another medicine used in treatment of pulmonary arterial hypertension is riociguat, a soluble guanylate cyclase stimulator, which in this mechanism increases cGMP production inter alia in pulmonary artery smooth muscle cells [56]. Riociguat significantly improves physical performance of patients with PAH, decreases pulmonary artery and systemic blood pressure, decreases pulmonary vessels resistance and increases cardiac output [56]. Considering that the endpoint of its mechanism of action is identical as the one of sildenafil, which is

increase of cGMP concentrations, it can be assumed that the one of riociguat in course of PAH and ARDS will be similar, however, some differences could be noticed. Chamorro et al. assessed the impact of riociguat and sildenafil on human pulmonary artery in vitro and rat pulmonary artery in vitro and in vivo [57]. In this study riociguat induced more potent vasodilatation than sildenafil in vitro and in vivo, in both human and rat models [57]. Moreover, under hypoxic conditions riociguat was approximately 3-fold more potent than under physiological oxygen levels. Researchers partially explained these findings by indication that NO needs oxygen for its formation and sildenafil only inhibits degradation of NO-induced cGMP, in contrast, riociguat directly stimulates guanylate cyclase and cGMP production [57]. Donda et al. show that riociguat reduces inflammation and vascular remodelling, therefore protects lungs in rat model of hyperoxia-induced lung injury [58]. However, this study has similar construction as these regarding sildenafil and shows only effects of riociguat in prevention of lung injury, not in treatment of disease-changed lungs. Therefore, in view of the study by Cornet et al., a significant vasodilatation induced by riociguat could lead to increase of lung ventilation/perfusion mismatch and decrease of blood oxygenation, thus deterioration of patient condition [51].

Riociguat could be helpful in treatment of COVID-19 associated ARDS, however, clinical studies evaluating its efficacy are needed and its introduction into the therapy should be considered and monitored very carefully due to the risk of increase of lung ventilation/perfusion mismatch and deterioration of patient condition in the first period of treatment.

6. Prostanoids

6.1. Epoprostenol

Epoprostenol is a synthetic prostacyclin, which through activation of prostaglandin E receptor 3 and IP receptor promotes cAMP production and reduces Ca2 + influx into cells [59]. This results in vasodilatation and inhibition of vascular smooth muscle cell proliferation, therefore, epoprostenol is often used in treatment of PAH [59]. Demerouti et al. in their analysis of PAH treatment indicated that epoprostenol reduces pulmonary artery blood pressure and significantly reduces patient mortality [59]. Interestingly, epoporostenol not only reduces proliferation of vascular smooth muscle cells but in high doses it induces their apoptosis by stimulation of Fas ligand production [60]. Possibly, this mechanism is responsible for observed increased vascular remodelling in form of plexiform lesions among patients with PAH treated with epoprostenol [60]. Despite this finding, improvement of patient condition and three-year survival rate makes epoprostenol a good therapeutic option in PAH [59,60]. Moreover, in murine ARDS model prostacyclin significantly attenuated lung infiltration by neutrophils and reduced inflammatory response by increase of IL-10 and decrease of TNF-α [61]. Furthermore, in clinical studies epoprostenol significantly improved blood oxygenation of patients with secondary ARDS, i.e. in course of sepsis or multiple trauma [62]. However, if administered to patients with primary ARDS i.e. in course of pneumonia, epoprostenol led to decrease of blood oxygenation [62]. This could be a result of the lowering of pulmonary artery blood pressure, which probably makes it more difficult for blood to penetrate into disease-changed parts of lugs. Moreover, results of inhibition of inflammation and pulmonary vessel remodelling could give positive clinical results a few days after epoprostenol administration at the soonest, therefore, this drug could be leading to transient deterioration of patient's condition but improvement in longer perspective. However, this hypothesis needs a confirmation in clinical studies. Although medical society recognises the potential of epoprostenol in treatment of COVID-19 associated ARDS there are still no studies assessing its effectiveness [63,64]. The induction of production of Fas ligand, which induces cell apoptosis, is an interesting feature of prostacyclin suggesting that through this mediator epoprostenol might inhibit SARS-CoV-2 proliferation. However, this is only another hypothesis highlighting the great need for comprehensive clinical research regarding treatment of SARS-CoV-2 induced ARDS.

6.2. Synthetic analogues of prostacyclin

Synthetic analogues of epoprotenol were created in order to modify pharmacokinetics of prostacyclin and make it possible to administer the drug by different routes, i.e. orally or by inhalation and increase drug half-time [65–67]. So far there are three drugs in this group: treprostinil, iloprost, and selexipag, which have been used in treatment of PAH with similar results as epoprostenol, which was expected, considering that they have the identical mechanism of action, even though they can stimulate adenylyl cyclase and reduce cell cytoplasmic calcium levels through different groups of receptors [65–67]. There is research reporting endothelium protection by Treprostinil, however, there is lack of studies investigating the effectiveness of epoprostenol analogues in treatment of ARDS [68]. Therefore, it is hard to assess the potential of treprostinil, iloprost or selexipag in treatment of COVID-19 associated lung injury but it should be corresponding to that of eporostenol.

7. Final comments

Regarding the study by Cornet et al. decrease of pulmonary blood pressure of patients with pulmonary lesions and impaired lung ventilation and perfusion can lead to increase of ventilation/perfusion mismatch and decrease of blood oxygenation [51]. Therefore, increased pulmonary artery blood pressure could be a defense mechanism sustaining a perfusion of disease-changed parts of lungs. However, disease and inflammation-related increased vessel permeability can lead to transudation, lung oedema and progressing respiratory failure. Therefore, in spite of the risky first phase of treatment with i.e. bosentan or sildenafil, targeted PAH therapy can be beneficial for patients with COVID-19 associated ARDS in long term through reduction of inflammation, oedema and lung damage. Worth noticing is the fact that synergism between epoprostenol and bosentan or sildenafil has been observed, therefore, a combination therapy should be considered in order to achieve a greater impact on patient's condition and utilise all specific features of these drugs, for example antiviral properties of bosentan and antiapoptotic o epoprostenol [69].

8. Conclusions

Endothelin receptor antagonists, phosphodiesterase 5 inhibitors, riociguat and prostacyclin with its synthetic analogues could be helpful in treatment of COVID-19, as their beneficial effect on lungs in ARDS was reported in many studies. All these drugs used in targeted therapy of PAH have proven ani-inflammatory effect and reduce pulmonary artery blood pressure, lung oedema and remodelling. Moreover, bosentan shows antiviral properties and sildenafil, as well as epoprostenol, inhibits apoptosis of lung epithelial cells. Considering a substantial number of studies bosentan, sildenafil and epoprostenol appear to be most promising as a treatment of COVID-19 associated ARDS and a combination of these drugs should be considered, as synergism between these pharmaceuticals was reported. However, so far there have only been few clinical studies on human subjects and among patients with lung lesions decrease of pulmonary blood pressure can lead to increase of ventilation/perfusion mismatch and decrease of blood oxygenation. Therefore, the targeted PAH therapy in treatment of COVID-19 associated ARDS could be a useful tool saving lives of patients with severe SARS-CoV-2 infection, however, its introduction should be investigated and monitored very carefully, as it can lead to transient deterioration of patient's condition.

CRediT authorship contribution statement

Oskar Puk: Conceptualization, Writing – original draft, Methodology. **Aleksandra Nowacka:** Writing – original draft, Literature search. **Klaudia Smulewicz:** Writing – original draft, Literature search. **Katarzyna Mocna:** Writing – original draft. **Wiktor Bursiewicz:** Writing – original draft, Project administration, **Validation Natalia Kęsy:** Writing – original draft. **Justyna Kwiecień:** Writing – original draft. **Michał Wiciński:** Project administration, Validation.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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