INTRODUCTION

The family Coronaviridae is comprised of numerous viruses infecting human and diverse animals including farm livestock and wild animals (cats, dogs, bats, cows, camels, pigs, birds, etc.). It consists of two virus subfamilies (Letovirinae and Orthocoronavirinae) including five genera and around 40 virus species [1]. The subfamily Orthocoronavirinae that contains human coronaviruses consists of four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. Coronaviruses (CoV) affect various organs and tissues and act as pathogens causing a broad range of diseases including severe human respiratory infection called atypical pneumonia. Usually, viruses of this family induce acute infection manifested by signs of inflammation featured with properties of cytokine storm syndrome [2, 3].

Coronaviruses are enclosed by a lipid envelope (enveloped viruses) and carry genomic positive-sense RNA, which is translated by host ribosomes and guides synthesis of viral proteins as well as sub-genomic RNAs and subsequent replication of the viral genome and assembly of viral particles [1, 4]. Depending on species, coronavirus genomic RNA consists of 25-30 · 10³ nucleotides and bears 22-29 viral genes encoding relevant proteins, four of which (N, S, M, E) play the major structural role in viral particles (Table). Moreover, several accessory viral proteins functioning as ion channels (viroporins) may also be found in virions [5].

Great interest in Coronaviridae has now been raised due to emergence of the dangerous type of human pneumonia caused by the novel *Betacoronavirus* strain SARS-CoV-2 [4]. This strain turned out to be close to bat SARS-like coronavirus as well as those inducing SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome), which caused in 2003 and 2012, severe pneumonia outbreaks in humans, referred as atypical pneumonia. Such infections did not induce a wide pandemic spread but showed a threatening pattern due to high mortality rate reaching up to 9.6-35.5% [2, 36]. Hence, the threat of the emerging
### Betacoronavirus genes, related proteins and their inhibitors

| Gene | Protein (domain) and size (a.a.) | Found in virion | Protein function | Viral protein inhibitor | Reference |
|------|----------------------------------|-----------------|-----------------|------------------------|-----------|
| 1ab<sup>3</sup> | (7096) | – | – | – | – |
| nsp1 | (180) | – | degradation of cell mRNAs, suppressed IFN | – | – |
| nsp2 | transmembrane protein (638) | – | activated NFKβ, augmented inflammation | – | – |
| nsp3<sup>4</sup> | transmembrane protein PLpro<sup>5</sup> (1945) | – | cysteine protease, downmodulated p53 and IFN induction | ritonavir/lopinavir | [6-9] |
| nsp4 | (500) | – | DMV formation | – | – |
| nsp5 | Mpro (306) | – | cysteine protease, downmodulated IFN | ritonavir/lopinavir | [6-9] |
| nsp6 | (290) | – | restricted autophagy, DMV formation | – | – |
| nsp7 | (83) | – | cofactor nsp8, nsp12 | – | – |
| nsp8 | (198) | – | cofactor nsp7, nsp12 | – | – |
| nsp9 | (113) | – | dimerization and RNA binding | – | – |
| nsp10 | (139) | – | platform for nsp12, nsp14 | – | – |
| nsp11 | (13) | – | (?)<sup>5</sup> | – | – |
| nsp12<sup>2</sup> | Pol (932) | – | RNA-dependent RNA polymerase | ribavirin/favipiravir | [10-12],[13] |
| nsp13 | (601) | – | RNA helicase, 5′-phosphatase | remdesivir | [6, 14, 15] |
| nsp14 | (527) | – | 3′→5′ exoribonuclease | – | – |
| nsp15 | (346) | – | endoribonuclease, dsRNA sensor | – | – |
| nsp16 | (298) | – | 2-O-MTase, MDA5 sensor, IFN pathway inhibitor | – | – |
| S | envelope protein (spike protein)<sup>3a</sup> (1278) | + | virus entry into target cells | protease inhibitors | [16-22]<sup>6</sup> |
| | | | | fusion-inhibiting peptides | [23]<sup>7</sup> |
| | | | | chloroquine antibodies | [24-26] |
| | | | | [27-32] |
| 3a | (275) | (?)<sup>3</sup> | augmented cytokine response and inflammation via NLRP3 | – | – |
| E | envelope protein (viroporin) (75) | + | ion channel, regulates virion assembly | chloroquine antibodies | [24-26] |
| M | viral matrix protein (222) | + | links viral envelope and nucleocapsid | – | – |
coronavirus pandemic corroborates the need to develop high-efficacy pharmaceuticals against coronaviruses, refining principles for using available antivirals and development of pathogenetic approaches to the treatment of disease.

Currently, there may be highlighted six essential chemical classes of drugs acting on diverse viral targets able to block coronavirus replication and suppress the development of disease. Such drug classes were designed based upon current knowledge about coronavirus replication and the pathogenetic mechanisms underlying coronavirus infection, and include: (1) viral polymerase inhibitors; (2) inhibitors of the viral protease Mpro, which participates in generation of active viral polymerase; (3) inhibitors of cell proteases involved in activation of CoV S protein that drives virus entry into target cells; (4) endosomal inhibitors of virus deproteinization; (5) preparations containing recombinant interferons α2 and β1; (6) preparations containing antiviral antibodies.

**VIRAL POLYMERASE INHIBITORS**

Viral polymerase is a standard therapeutic target, and its blockade inhibits replication of the viral genome and thus suppression of replication of the virus. By now, there are diverse multi-specific RNA polymerase inhibitors acting on various viruses due to marked structural and functional similarities of this enzyme existing among different viruses [37]. Ribavirin (furanosyl carboxamide) is among inhibitors of this type because it exhibits high activity against diverse viruses [10] (including coronaviruses) at concentration of 10–25 nM (IC50), with selectivity index of more than 100 [10-12]. Because SARS, MERS, and COVID-19 (coronavirus disease 2019) mainly develop in the respiratory tract cells, ribavirin aerosol inhalations that could create effective antiviral activity at non-toxic concentrations in the airway epithelial layer and thus might serve as the most appropriate drug formulation.

This is based on low pulmonary bioavailability shown for oral vs. aerosol ribavirin (1% and more than 70%, respectively) and its subsequent activation via a phosphorylation reaction occurring in the respiratory epithelium [12]. Of note, direct aerosol-delivered action on respiratory epithelium might be most active and efficient at an early stage after the onset of infection, which is accompanied by virus replication at eclipse phase when pathological events of inflammation and edema would have not reached a dangerous level.

**Favipiravir** and its ribosylated derivatives might be other candidate drugs fighting against coronaviruses [13]; they exhibit high antiviral potential and selectivity index with regard to diverse RNA-bearing viruses [13]. On the other hand, **remdesivir** derived from phosphorylated 1’-cyano substituted adenosine is a broad-spectrum drug displaying high antiviral potential at IC50 ranging within 50–70 nM against diverse viruses including coronaviruses [14, 15]. This drug is undergoing the final phase of clinical trials [6].
INHIBITORS OF CORONAVIRUS PROTEASE Mpro

Translation of viral RNA generating a lab polypeptide (MM ~750 kDa) that undergoes autoproteolytic cleavage into 14-16 fragments (nsp1-nsp16), depending on viral type, may function as an active viral polymerase and regulate replication of the viral genome and subsequent synthesis of viral proteins in the first stage of coronavirus replication after entering target cells [1]. It turned out that cleavage of the polyprotein pp1ab (PLpro), also bearing cysteine protease papain-like domain [35]. Lopinavir/ritonavir simulating proteolytic enzymes within the polyprotein 1ab are performed by protein nsp3 vir (“Kaletra”) [6-9]. In some viruses, two initial breaks sensitive to the binary protease inhibitor lopinavir/ritonavir close to picornavirus and HIV proteases [38] and being Mpro) exerting specificity of the target proteolytic sites out that cleavage of the polyprotein 1ab (pp1ab) is mediated by its own domain 5 (nsp 5) (called protease domain Mpro) exerting specificity of the target proteolytic sites close to picornavirus and HIV proteases [38] and being sensitive to the binary protease inhibitor lopinavir/ritonavir (“Kaletra”) [6-9]. In some viruses, two initial breaks sensitive to the binary protease inhibitor lopinavir/ritonavir close to picornavirus and HIV proteases [38] and being Mpro) exerting specificity of the target proteolytic sites.

INHIBITORS OF VIRAL CELL ENTRY

Chloroquine has been widely used in medical practice for treatment of malaria. This drug exhibits pronounced activity against coronaviruses in cell culture and animal models [24]. The mechanism of its action against multiple viruses including Betacoronaviruses is mediated by elevated acidic pH value inside cell endosomes that interferes with pH-dependent conformational transition of viral fusion proteins (coronavirus S protein) into their active state thus resulting in retarded virus deproteinization (viral uncoating) inside cell endosomes and prevents further infection of target cells; additionally, this drug may alter glycosylation of cell receptors including ACE2 used by SARS-CoV and SARS-CoV-2 for entry [25]. Based on this platform, chloroquine was recommended for treatment of COVID-19, and it demonstrated positive effects in some patients in China [26].

COMPOUNDS CONTAINING SPECIFIC ANTIVIRAL ANTIBODIES

This approach to therapy of coronavirus infection implies administration of antibodies able to neutralize infectious properties of this virus. In addition, inoculation of antibodies might also be used for early disease prevention called passive immunization. Two essential opportunities are available for using antiviral antibodies [28-30]: (i) design and generation of tailored virus-neutralizing antibodies (or their active antiviral domains) by using gene engineering and biotechnology. Such preparations specific to coronaviruses including SARS-CoV-2 have not yet been created [27]; (ii) a specific antiviral immunoglobulin preparation obtained via a more traditional and simpler technique from convalescent subjects who recovered after coronavirus infection including COVID-19 or from animals vaccinated with SARS-CoV-2 or its components [31, 32]. The first observations have been reported of successfully administered antiviral immunoglobulins purified from convalescent subjects with MERS and COVID-19, which were used for treatment of atypical pneumonia in China during 2020 SARS-CoV-2 outbreak [43]. Preparations containing antiviral antibodies should be used with some caution, because coronavirus infectiveness to immune cells was noted to be augmented by some types of artificial antibodies targeting CoV S protein [44]. Fortunately, such antibodies have not been identified yet in sera from convalescent subjects [31]. Moreover, successful
administration of such preparations should require that convalescent serum immunoglobulins would contain high titer (1/80) of anti-CoV antibodies assessed by HI test [32].

INTERFERON PREPARATIONS

Preparations containing human recombinant interferon α2 and β1 classes were used in therapy of closely-related infections caused by SARS-CoV, MERS-CoV, and SARS-CoV-2 [45, 46]. It was found that interferon β1 exerted slight curative effects, whereas interferon α2 revealed no activity, but the most prominent activity was observed after using interferon β1 in combination with ribavirin [6, 11, 46]. While choosing a treatment strategy, it should be taken into consideration that interferon preparations may exhibit peak efficacy solely at early disease stages, when host reaction has not yet been augmented too much or culminated [2, 47, 48]. Moreover, use of exogenous interferon-based preparations would hardly be rational at later disease stages due to the high quantity of endogenous interferons produced in response to acute coronavirus infection. Finally, inoculation of exogenous interferon-based preparations at late stages of infection by further elevating pre-set high level of endogenous interferons could promote cytokine storm syndrome and inflammation at the site of infection, thereby deteriorating the disease course [3, 48].

COMBINATION THERAPY

The combined use of several drugs (pharmaceuticals) acting on various phases of the virus reproductive cycle or disease pathogenesis called a combination therapy was also administered to treat coronavirus infection. A positive curative effect was observed while administering ribavirin, interferon β1, and lopinavir/ritonavir [6, 11, 46]. This approach allows: (i) improving therapeutic efficacy, (ii) reducing drug dosing, (iii) preventing emergence of dangerous viral mutants with augmented virulence. It is known that a risk of developing viral mutants in an infected host is minimized when applying combination therapy [49].

RELATIONSHIP OF ETIOTROPIC AND PATHOGENETIC EVENTS IN THERAPY OF VIRAL DISEASES

Two major stages can be distinguished within the timeframe of developing acute viral disease. The early (etiotropic) phase dominated by virus replication is called the exponential phase of virus propagation and accumulation (day 7–10 from the onset of viral infection). It is characterized by emergence of developing virus-specific defense reaction to infected host cells (production of immunoglobulins, antigen-specific T and B cell clones, and interferons) and general inflammatory response due to cytokines and chemokines synthesized at the site of infection. Later, growth of the virus declines and this results in developing a pathogenetic phase associated with formation of pathologic mechanisms critically affecting disease outcome as well as posing a threat of potential complications. Among the latter are exuberant inflammation, developing acute respiratory distress syndrome, lung edema and hypoxia, as well as emergence of infections caused by pathogenic microbes and sepsis [2, 3, 50].

Owing to a two-phase pathogenesis in viral diseases, it is reasonable to build a proper therapeutic strategy. In particular, specific antivirals should be available in the therapeutic arsenal and dominate in treatment during the etiotropic phase. In the case of coronavirus it can be referred to as the phase for use of lopinavir/ritonavir, aerosol ribavirin inhalation, injection of virus-specific antibodies and inhibitors of host proteases, and interferon preparations (particularly interferon β1, see above the corresponding sections). On the contrary, the pathogenetic phase should rely on a therapeutic strategy aimed at restriction or relief of pathological life-threatening mechanisms by taking into consideration patient condition and severity of pathological events, mainly to eliminate intoxication, reduce lung edema, and improving blood oxygenation to compensate for lung failure, mostly by extracorporeal membrane oxygenation of blood (ECMO) for avoiding rupture of swollen lungs in case of involuntary inhaled oxygen therapy. In addition, anti-inflammatory drugs should be also used during this phase to recover respiratory function by paying special attention to antibacterial therapy to prevent emerging secondary bacterial pneumonia and concomitant sepsis [51, 52].

On the other hand, it might not seem very reasonable to use antivirals during a pathogenetic phase of infection for two main reasons: (i) specific antiviral antibodies as well as B and T cell clones inhibiting virus growth and removing host infected cells have been already formed by the onset of this phase [3, 32, 48], and (ii) avoiding use of such drugs would contribute to lowering their toxic side-effects on developing mature immune response that includes specific antibodies, T and B cell clones, as well as interferon response. However, it should be noted that coronavirus disease might potentially be exacerbated due to virus evolution and continuous replacement of the initial parental virus in a single host. Such a phenomenon was described for Betacoronavirus, so that a more virulent within-patient virus strain may emerge during disease progression that could markedly aggravate it and pose a threat to the patient’s (or animal’s) life [53–55]. Hence, in the case of developing impaired immune response and signs of residual viral infection, administration of antivirals should be continued to lower a risk of developing higher virulence viral
It seems important that a combination therapy affecting various targets in viral growth should be appropriate to use even at early the phase of infection in order to efficiently prevent emergence of highly virulent viral mutants.

**Betacoronavirus**, including SARS-CoV-2, elicits infection of the respiratory tract often ending with the development of lung edema, severe hypoxia, and sepsis. Two phases referred as etiotropic and pathogenetic can be highlighted in disease pathogenesis. During the first stage, virus growth and accumulation dominate, which is accompanied by appearance of initial pathological disturbances in the respiratory tract. However, during the second stage virus propagation declines, but pathological events mainly manifested as excessive inflammation and lung edema develop as a secondary consequence of virus-induced cytopathic effects. Whereas in the first stage it is justified to use pharmaceuticals and their combinations (aerosol ribavirin inhalation, lopinavir/ritonavir, protease inhibitors, interferon compounds, antiviral antibodies) aimed at suppressing diverse targets during virus propagation, during the second disease stage it might be important and reasonable to rely on administration of pathogenetic drugs to restrict life-threatening events resulting in marked inflammation, intoxication, hypoxia, secondary pneumonia, and sepsis.

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