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Review

Therapeutic Targets in the Virological Mechanism and in the Hyperinflammatory Response of Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2)

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Abstract: This work is a bibliographic review. The search for the necessary information was carried out in the months of November 2022 and January 2023. The databases used were as follows: Pubmed, Academic Google, Scielo, Scopus, and Cochrane library. Results: In total, 101 articles were selected after a review of 486 articles from databases and after applying the inclusion and exclusion criteria. The update on the molecular mechanism of human coronavirus (HCoV) infection was reviewed, describing possible therapeutic targets in the viral response phase. There are different strategies to prevent or hinder the introduction of the viral particle, as well as the replicative mechanism ((protease inhibitors and RNA-dependent RNA polymerase (RdRp)). The second phase of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) involves the activation of hyperinflammatory cascades of the host's immune system. It is concluded that there are potential therapeutic targets and drugs under study in different proinflammatory pathways such as hydroxychloroquine, JAK inhibitors, interleukin 1 and 6 inhibitors, and interferons.

Keywords: SARS-CoV-2; COVID-19; ACE2; protease inhibitors; RdRp inhibitors; JAK inhibitors; interleukin 1 inhibitors; interleukin 6 inhibitors; interferon

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1. Introduction

The human coronavirus (HCoV) family can cause infections in humans, being a zoonotic disease, as it is transmitted from animals (birds and mammals) to humans [1]. The symptoms shown by patients affected by HCoV vary between processes that resemble the common cold to severe conditions such as those described with severe acute respiratory syndrome coronavirus 1 [2] (SARS-CoV-1) and Middle East respiratory syndrome coronavirus virus (MERS-CoV) [3].

There are drugs with indications in other pathologies that are being tested in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; of particular interest are those that have been shown to be effective in other coronaviruses such as SARS-CoV-1 and MERS-CoV. Two main phases have been differentiated: a viral response and a hyperinflammatory response. This article reviews different strategies to prevent or hinder the introduction of the viral particle, as well as the replicative mechanism ((protease inhibitors (PI), inhibitors of RNA-dependent RNA polymerase (RdRp) (RNA-dependent RNA polymerase), and inhibitors of intracellular transport of viral structures) [1–3].

2. Materials and Methods

The preparation of this work was carried out through a systematic bibliographic review of the articles found by searching the following databases: Medline/Pubmed, WOS, Scielo, Scopus, and Google Scholar. To find the best possible scientific evidence, a series of inclusion and exclusion criteria were applied.

The keywords for this review are as follows: SARS-CoV-2, COVID-19, ACE2, protease inhibitors, RdRp inhibitors, JAK inhibitors, interleukin 1 inhibitors, interleukin 6 inhibitors, and interferon. To carry out the bibliographic search, different keywords in English were used: "SARS-CoV-2", "COVID-19", "ACE2", "protease inhibitors", "RdRp inhibitors", "JAK inhibitors", "interleukin 1 inhibitors", "interleukin 6 inhibitors", and "interferon". These have been validated by the DeCS and MeSH. Once selected, the corresponding Boolean operators, AND/OR, were used, as well as the necessary parentheses and quotation marks. The final search string is as follows: (SARS-CoV-2) OR (COVID-19) AND (ACE2) AND (protease inhibitors) AND (RdRp inhibitors) AND (JAK inhibitors) AND (interleukin 1 inhibitors) OR (interleukin 6 inhibitors) AND (interferon). The criteria that were taken into account for the selection of the relevant studies were the following. Inclusion criteria: the period between 2010 and 2023; article type: article review and article research; field: medicine; English language; sample in adult population; and studies that provide scientific evidence justified by the level of indexing of articles in journals according to the latest certainties. Exclusion criteria: articles prior to 2010; language: not English; studies in which the population was minors; and studies that do not provide scientific evidence justified by the level of indexing of articles in journals according to the latest certainties.

For the methodological evaluation of the individual studies and the detection of possible biases, the evaluation was carried out using the PEDro Evaluation Scale. This scale consists of 11 items, providing one point for each element that is fulfilled. The articles that obtained a score of 9–10 points have an excellent quality, those between 6 and 8 points have a good quality, those that obtained 4–5 points have an intermediate quality, and finally those articles that obtained less than 4 points have a poor methodological quality.

The Scottish Intercollegiate Guidelines Network classification was used in the data analysis and assessment of the levels of evidence, which focused on the quantitative analysis of systematic reviews and the reduction in systematic error. Although it took into account the quality of the methodology, it did not assess the scientific or technological reality of the recommendations.

3. Fundamental Structural Proteins

The HCoV genome encodes four fundamental structural proteins [4], which are necessary to form the viral particle:

The spike (S): responsible for the union of HCoV with host cell receptors, facilitating viral entry [5–7]. The union of the virus with angiotensin converting enzyme type II (ACE2) constitutes the point of entry to infect human cells, with this union being primed by the transmembrane protease, serine 2 (TMPRSS2) [8,9].

The nucleocapsid (N): binds to the ribonucleic acid (RNA) genome of HCoV, forming the nucleocapsid [10].

Membrane protein (M): the most abundant structural protein that interacts with other structural proteins for the assembly of the viral envelope [11].

The envelope (E): during replication, it is abundantly expressed in the endoplasmic reticulum, Golgi apparatus, and the endoplasmic reticulum–Golgi intermediate compartment (ERGI), although it is only expressed in small amounts in the envelope of the virion [12,13]. In the absence of protein E, reduced titers of viral particles are observed and viral maturation is prevented with incompetence for propagation. This has been observed in vitro with recombinant HCoVs lacking protein S [14–18].

Any of these proteins can be the basis of future vaccines against SARS-CoV-2. In the race to manufacture the anti-SARS-CoV-2 vaccine [19], there are more than 125 anti-SARS-CoV-2 vaccine candidates [20].

4. Envelope Protein

The envelope protein E is a short transmembrane protein of 76–109 amino acids (8.4–12 kDa) [21–23], consisting of a short amino-terminal (7–12 aa) hydrophilic end; followed by a transmembrane domain (25 aa) hydrophobic, where there is an amphipathic α-helix with prop-

erties of forming an ion conducting pore [24–26]; and a long carboxy-terminal end [27–30]. It can establish homotypic interactions, forming transmembrane-domain-dependent homo-oligomeric multimers [31] and generating a known ion channel protein known as viroporin [32,33].

Although many HCoVs encode two proteins that, when homooligomerized, can form viroporins, SARS-CoV1 encodes three proteins: 3a, E, and 8a. Proteins 3a and E contain a PDZ-binding motif (PBM), which can bind to more than 400 cellular proteins that contain a PDZ domain [34,35].

5. Biochemical–Molecular Mechanism of HCoV Infection

Analogous to what was known about the virology of SARS-CoV-1 and MERS, the proposed mechanism is defined [36,37] (Figure 1):

1. Binding of the spike protein (S) virus of SARS-CoV-2 with the angiotensin converting enzyme type II (ACE2), constituting the point of entry to infect human cells, with the said union being primed by the transmembrane protease, serine 2 (TMPRSS2) [8,9].
2. Endocytosis of viral particles.
3. Early translation of the positive ribonucleic acid (RNA) of SARS-CoV-2 as if it were host cell mRNA with the synthesis of early (regulatory) proteins, including polyproteins and essential viral proteases.
4. Proteolysis through a protease. The polyproteins (pp1a and pp1ab) are cleaved into 16 nonstructural effector proteins by 3CLpro and PLpro.
5. Formation of the replication complex together with the RNA-dependent RNA polymerase (RdRp).
6. Synthesis of negative single-stranded RNA from the positive single-stranded RNA template by RNA polymerase, with formation of the replicative complex. The negative single-stranded RNA is not released, remaining associated with the replicative complex.
7. The replicative complex produces synthesis of positive single-stranded RNA, mRNA, and negative single-stranded RNA.
8. Late translation of positive single-stranded RNA and mRNA, with late (structural) protein synthesis on the ribosomes of the rough endoplasmic reticulum.
9. Formation of viral particles with assembly in the ERGI intermediate compartment (endoplasmic reticulum–Golgi apparatus).
10. Release of viral particles by exocytosis.

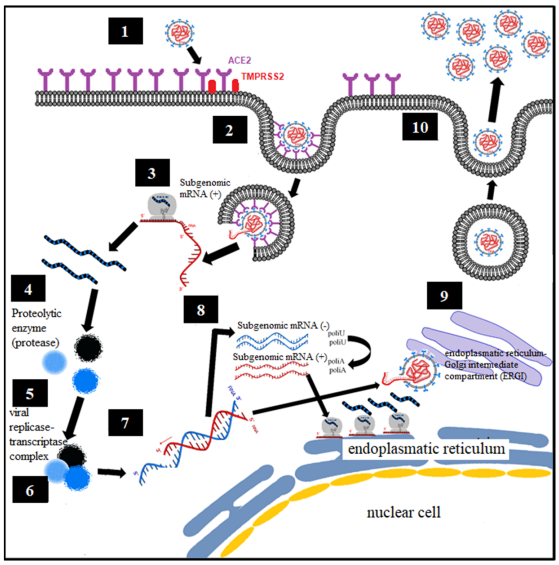

Figure 1. Virological mechanism of SARS-CoV-1 and MERS-CoV.

6. Etiopathogenic Phases of COVID-19

According to epidemiological data from the World Health Organization, the first variants of SARS-CoV-2 are as follows: Alpha (B.1.1.7) (United Kingdom, 12/2020), Beta (B.1.351) (South Africa 12/2020), Gamma (P.1) (Brazil, 01/2021), Delta (B.1.617.2) (12/2020), and Ómicron (B.1.1.529) (South Africa, 11/2021) [38].

In COVID-19, an etiopathogenic model has been proposed that divides it into a response phase against SARS-CoV-2 and a host inflammatory response phase where an inflammatory cascade occurs [39]. Figure 2 shows the three stages: (I) early infection (which corresponds to the viral response phase), (II) or pulmonary phase (where the two response phases overlap), and (III) or hyperinflammatory phase. Depending on the phase in which the patient is, he will have a different therapeutic approach.

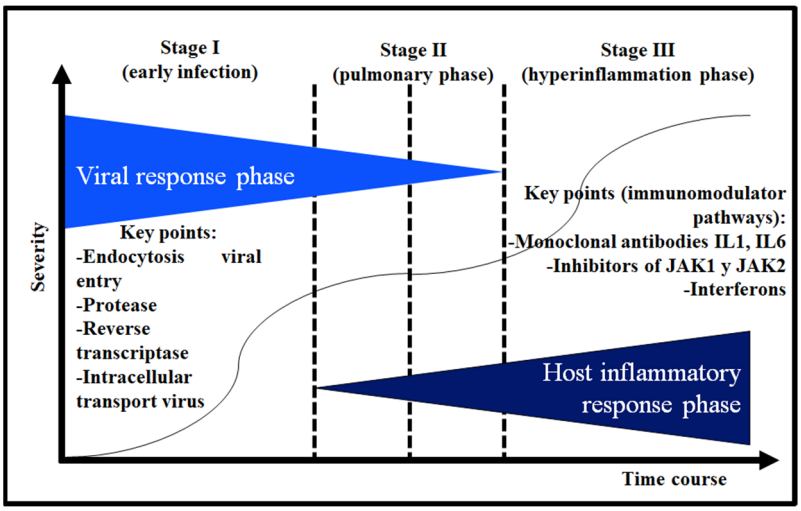

Figure 2. Differentiated phases of viral and proinflammatory response (interleukin 1: IL 1; interleukin 6: IL-6; Janus kinase: JAK).

In a didactic way, in the viral response phase, a subdivision could be made into the following: (a) entry of the viral particle, (b) proteolysis, (c) SARS-CoV-2 RNA replication by RNA-dependent RNA polymerase, and (d) intracellular transport of viral structures (Figure 2) [38,39].

7. Physiopathology of Edema in Pulmonary Alveoli and Possible Therapeutic Targets

Under physiological conditions, edema in the pulmonary alveoli is resolved by the action of three proteins (Figure 3) [40]:

- The Na^+/K^+ ATP-ase pump, which allows two K^+ ions to enter intracellularly and three Na^+ ions to exit the cell by active transport.
- The epithelial channel of Na^+ ions sensitive to amiloride (ENaC) (amiloride-sensitive sodium channel), which allows the transport of Na^+ by facilitated diffusion. They are distributed in organs such as the lung, large intestine, kidney, vascular endothelium, and placenta.
- Cystic fibrosis transmembrane conductance regulator (CFTR), which belongs to the ABC transporters and exerts its function through primary active transport.

Given the current SARS-CoV-2 epidemic, a possible therapeutic target for the pathology caused by HCoV could be the identification of drugs that interrupt the PBM–PDZ junctions, as these pathways would be involved in the pathophysiology of the infection. Protein E may be the origin of the future vaccine. Viroporins are viral proteins with ion channel activity that play important roles in various processes, including virus replication and pathogenesis.

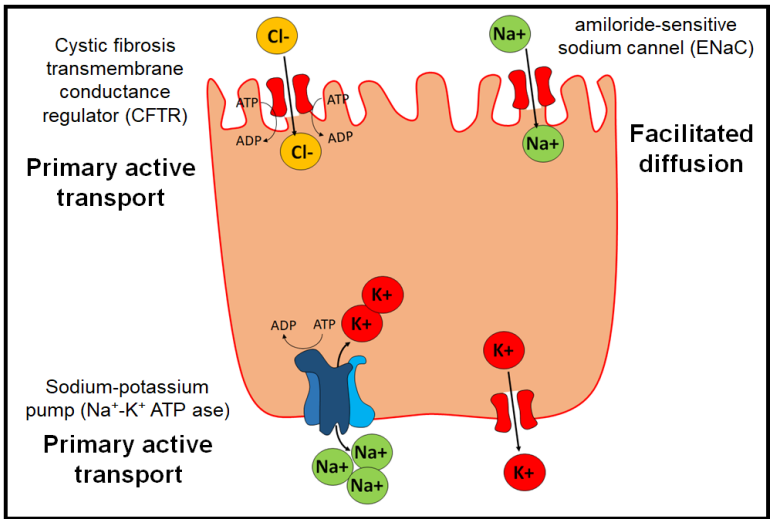

Figure 3. Physiological transporters that prevent edema in pulmonary alveoli.

8. Therapy in the Viral Response Phase

8.1. Inhibitors of Viral Particle Entry

8.1.1. TMPRSS2 Inhibitors

The SARS-CoV-2 spike (S) protein binds to ACE2, which is the entry point for infecting human cells, requiring TMPRSS2 [8,9]. The entry of SARS-CoV-2 into the cell could be blocked by both protein S neutralizing antibodies and TMPRSS2 inhibitors. Among the latter are camostat mesylate [41] (used as a treatment for chronic pancreatitis [42]) and nafamostat [43].

8.1.2. Arbidol

Umifenovir (Arbidol®) binds to the hemagglutinin of the influenza virus [44] and its inhibitory power has been demonstrated in the Zika Virus [45]. Three-dimensional analysis of molecular structure using HADDOCK2.2 (https://haddock.science.uu.nl/ (accessed on 26 March 2023)) and SwissDock (http://swissdock.ch/docking (accessed on 26 March 2023)) servers shows binding of arbidol to trimers of the glycoprotein S of SARS-CoV-2 [46]. The usefulness of this drug has been proven as it interferes with and inhibits membrane fusion with the viral envelope [47].

8.1.3. Antimalarials

In addition to the immunomodulatory effect of the inflammatory cascade that we will see later, antimalarials (hydroxychloroquine (HCQ) and chloroquine (CQ)) have a direct antiviral effect by interfering with the binding of the viral particle to ACE2 (altering the glycosylation of the receptor) [48] or with endocytosis (by increasing the pH of these organelles) [49].

8.1.4. Janus-Associated Kinase (JAK) Inhibitors

Baricitinib (Olumiant®) is a JAK inhibitor used in rheumatoid arthritis [50], which could inhibit endocytosis using a three-dimensional virtual model [51]. In addition, it participates in the immunomodulation of the inflammatory cascade [52,53].

8.1.5. Oseltamivir

Oseltamivir (Tamiflu®) binds to the neuraminidase of the influenza virus [54], which could be useful in patients with SARS-CoV-2 co-infection, although this virus does not require neuraminidase for cell entry.

8.1.6. Monoclonal Antibodies (MAbs) Directed against a Viral Coat Protein

Similarly to palivizumab against respiratory syncytial virus (RSV), the design of a monoclonal antibody (AbMo) directed against SARS-CoV-2 [55,56] could be a therapeutic option in the future.

8.1.7. ACE2 Soluble Receptor

It is based on the design of a recombinant protein similar to ACE2 that contains only the sequence of amino acids to which SARS-CoV-2 binds [57]. The virus would compete for binding to this protein and to ACE.

A scheme of the possible pharmacological mechanisms of action in the interference of SARS-CoV-2 entry is presented in Figure 4.

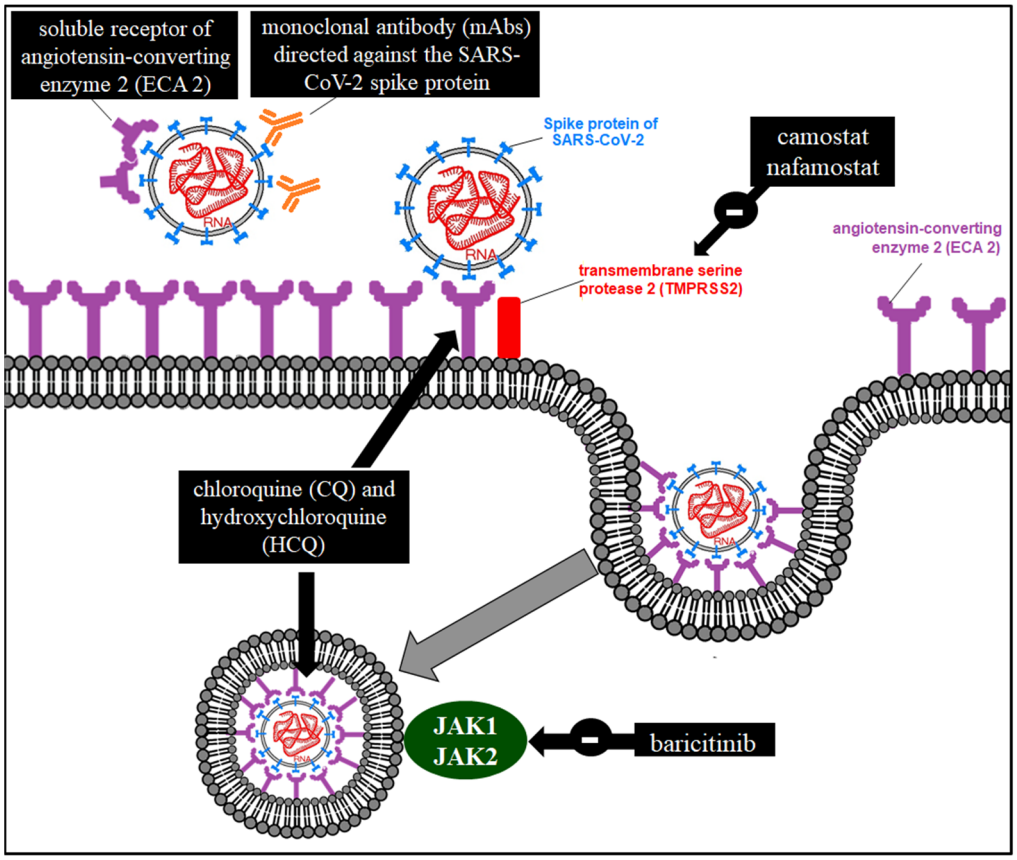

Figure 4. Possible pharmacological mechanisms of action in the interference of SARS-CoV-2 entry.

8.2. RdRp Inhibitors [58]

Its mechanism of action is by inhibition of RdRp, with some drugs being represented in Figure 4.

Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide, Avigan®) is a purine nucleotide prodrug (favipiravir ribofuranosyl-5-triphosphate) that inhibits the RdRp of influenza viruses [59,60], Ebola virus, hemorrhagic fever [61], and HCoV. Remdesivir (RDV) is a prodrug of a nucleotide analog (adenosine C nucleoside) developed as a treatment for Ebola virus infection [62] that showed inhibitory power against SARS-CoV and MERS-CoV in vitro [63]. It has been studied in monotherapy [64] and associated with chloroquine [65] in COVID-19. Ribavirin is a guanosine analog used for hepatitis C virus (HCV), which has been used in combination with lopinavir/ritonavir or interferon (IFN) in SARS-CoV1 and MERS [66]. Sofosbuvir is a pharmacologically active uridine nucleotide triphosphate prodrug (GS-461203) that acts as a pan-genotypic inhibitor of HCV RdRp NS5B, indicated for chronic hepatitis in adults. Ledipasvir targets the nonstructural HCV phosphoprotein

NS5A, essential for RNA replication and virion assembly. The combination of sofosbuvir with ledipasvir (Harvoni®) or velpatasvir can inhibit both RdRp and PI [67] of SARS-CoV-2. Galidesivir and tenofovir have been shown in molecular studies to inhibit RdRp [68].

8.3. Protease Inhibitors (PIs)

Its mechanism of action is by inhibition of the proteases represented by some drugs in Figure 1.

Velpatasvir is a pan-genotypic inhibitor of the HCV NS3/4A protease described in the previous section [67], while lopinavir is an inhibitor of the protein, similar to 3-chymotrypsin as the protease of the human immunodeficiency virus (HIV), reducing the maturation of viral particles. It is marketed together with ritonavir (Kaletra®), which inhibits the metabolism of lopinavir [69]. It has been used in COVID-19 [70]. Darunavir also acts in a similar way to lopinavir [69,70].

8.4. Inhibitors of Intracellular Transport of Viral Structures

The importin protein is formed by a heterodimer of two subunits (alpha and beta-1) (IMPα/β1) [71] participating in the nuclear transport models of SARS-CoV-2. Studies on its efficacy and safety in COVID-19 are needed. Ivermectin demonstrated inhibition of nuclear transport; either from the non-structural protein 3 (NS3) of flavivirus [72], NS5 of the dengue virus [73], or of the MxA factor of the influenza A virus [74]. In vitro inhibition of SARS-CoV-2 replication has been demonstrated [75].

9. The Hyperinflammatory Response in Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) Infection

There is no time for the development of specific drugs for the treatment of coronavirus disease 2019 (COVID-19) (coronavirus disease-2019) [1]. There are drugs with indications in other pathologies that are being tested in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; of particular interest are those that have been shown to be effective in other coronaviruses such as severe acute respiratory syndrome coronavirus 1 [2] (SARS-CoV-1) and Middle East respiratory syndrome coronavirus [3,4] (MERS-CoV) (Middle East respiratory syndrome coronavirus). Two main phases of the patient's response to infection have been differentiated: a viral response and a hyperinflammatory response. This article reviews different strategies to prevent or hinder the hyperinflammatory response of the eukaryotic host cell.

10. Therapy in the Hyperinflammatory Response Phase with Immunomodulators of the Immune Inflammatory Cascade

10.1. Glucocorticosteroids

Glucocorticosteroids (GCs) regulate the expression of anti-inflammatory proteins in the nucleus (transactivation) and repress the expression of proinflammatory proteins (tranrepression), exerting a potent anti-inflammatory effect [76,77].

10.2. Antimalarials

Antimalarials (hydroxychloroquine (HCQ) and chloroquine (CQ)) have an immunomodulatory effect by increasing the lysosomal pH in antigen-presenting cells (APCs) and by interfering with Toll-like receptor (TLR) signaling (Toll-like receptors) at the level of the innate immune response. They also decrease the production of proinflammatory cytokines (interleukin 1 (IL-1—interleukin-1), interleukin 6 (IL-6—interleukin 6), tumor necrosis factor alpha (TNFα), and interferon-gamma (IFNγ)) [78] of the COVID-19 storm. Its efficacy has been described in COVID-19 either in monotherapy [79] or associated with azithromycin [80,81]. Attention should be paid to cardiovascular effects [82].

10.3. Janus Kinase Inhibitor (JAK 1 and 2)

The anti-inflammatory effect of baricitinib (Olumiant®) is due to the reversible inhibition of JAK 1 and 2 through a signal transduction pathway involving STAT proteins [83], which modulates the expression of genes associated with inflammation in immune cells and inhibits IFN production. In addition, it may have a possible antiviral effect by inhibiting AP2-associated protein kinase 1 (AP2-associated protein kinase 1) [84], interrupting the passage of SARS-CoV-2 within the cell and even the intracellular assembly of the viral particles (Figure 5).

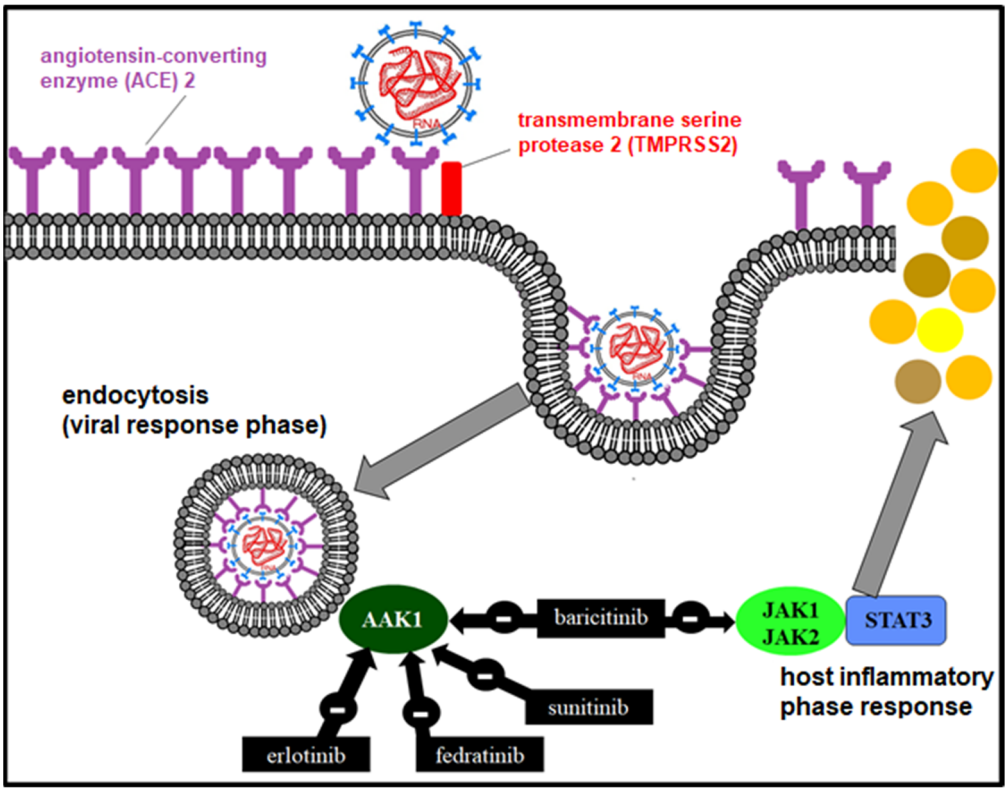

Figure 5. Mechanism of action of JAK1/2 and AAK1 inhibitors in the viral and inflammatory phase.

Baricitinib is approved in more than 65 countries for the treatment of moderate–severe rheumatoid arthritis (RA). It is useful in reducing mortality in COVID-19 by associating it with different antivirals [85]. RECOVERY included 8156 patients with COVID-19 treated with baricitinib versus usual care between 2 February 2021 and 29 December 2021. Baricitinib significantly reduced the risk of death in hospitalized patients by 20% [86].

Erlotinib, another JAK inhibitor, has shown pharmacokinetic efficacy in combination with ritonavir [87].

10.4. Blockers of the IL-1-Mediated Inflammatory Response

10.4.1. Anakinra (Kineret®)

Monoclonal antibody (mAb) is antagonistic to the human IL-1 receptor (r-metHuIL-1ra), produced in Escherichia coli cells by recombinant DNA technology. It is indicated in rheumatoid arthritis, cryopyrin-associated periodic syndrome (CAPS) (including Muckle-Wells syndrome (MWS), neonatal multisystem inflammatory disease (NOMID) (neonatal-onset multisystem inflammatory disease), chronic infantile neurological cutaneous and articular syndrome (CINCA), and severe manifestations of familial cold autoinflammatory syndrome (FCAS) and familial cold urticaria (FCU) (familial cold autoinflammatory)), and Still's syndrome. Its usefulness has been described in critical clinical cases where there is a cytokine storm such as macrophage activation syndrome (MAS) and secondary lymphohis-

tiocytic hemophagocytosis (SHLH) (secondary hemophagocytic lymphohistiocytosis). Its use in COVID-19 has been associated with increased survival [88].

10.4.2. Canakinumab (Illaris®)

Recombinant human IgG1κ anti-IL-1 beta mAb [89], listed in CAPS [90] (MWS, NOMID, CINCA, FCAS, and FCU), as well as tumor-necrosis-factor-receptor-associated periodic syndrome (TRAPS) (tumor-necrosis-factor-receptor-associated periodic syndrome), hyperimmunoglobulin D syndrome (HIDS), mevalonate kinase deficiency (MKD), familial Mediterranean fever (FMF), familial Mediterranean fever Still, and arthritic gout.

10.4.3. Rilonacept (Arcalyst®)

Dimeric fusion protein with ligand-binding domains of the extracellular portions of the human interleukin 1 receptor type I (IL-1RI) receptor and of the IL-1 receptor accessory protein (IL-1) (1RAcP) (interleukin-1 receptor accessory protein) bound in line to the Fc portion of human IgG1 [89]. By binding to the proinflammatory cytokines IL-1α and IL-1β and antagonizing the endogenous IL-1 receptor (IL-1ra), it blocks the inflammatory cascade (Figure 6).

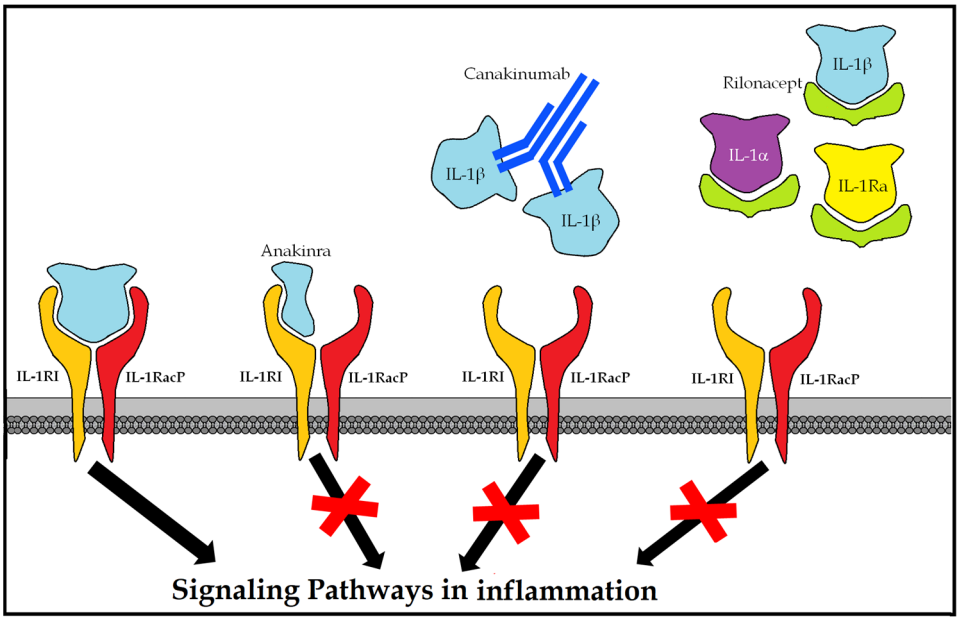

Figure 6. Therapeutic options for blocking the hyperinflammatory response mediated by IL-1.

10.5. Blockers of the Inflammatory Response Mediated by IL-6

10.5.1. Tocilizumab (Actemra®/RoActemra®)

Recombinant human IgG1 mAb against interleukin 6 receptor (IL-6R) that binds soluble and membrane-bound receptors. It is indicated in combination with methotrexate (MTX) in adults with severe, active, and progressive rheumatoid arthritis (RA) not previously treated with MTX, or in moderate to severe active RA with inadequate response or intolerance to prior treatment with one or more disease-modifying antirheumatic drugs (DMARDs) or tumor necrosis factor (TNF) antagonists; that is, systemic juvenile idiopathic arthritis (sJIA) and polyarticular (pJIA) and giant cell arteritis (GCA) [91].

10.5.2. Sarilumab (Kevzara®)

Recombinant human IgG1 anti-IL 6R mAb binds both soluble and membrane-bound receptors, inhibiting IL-6 cell signaling transmission measured as STAT-3 inhibition. It is indicated in moderate to severe active rheumatoid arthritis (RA) in adults who are

inadequate responders to, or intolerant to, one or more disease-modifying antirheumatic drugs (DMARDs) [92].

10.5.3. Siltuximab (Sylvant®)

Chimeric human-murine IgG1κ anti-IL-6 mAb forms stable, high-affinity complexes with soluble forms of IL-6. It is indicated for the treatment of multicentric Castleman's disease (MCD) in adults negative for human immunodeficiency virus (HIV) [93] and human herpesvirus-8 (HVH8) (Figure 7).

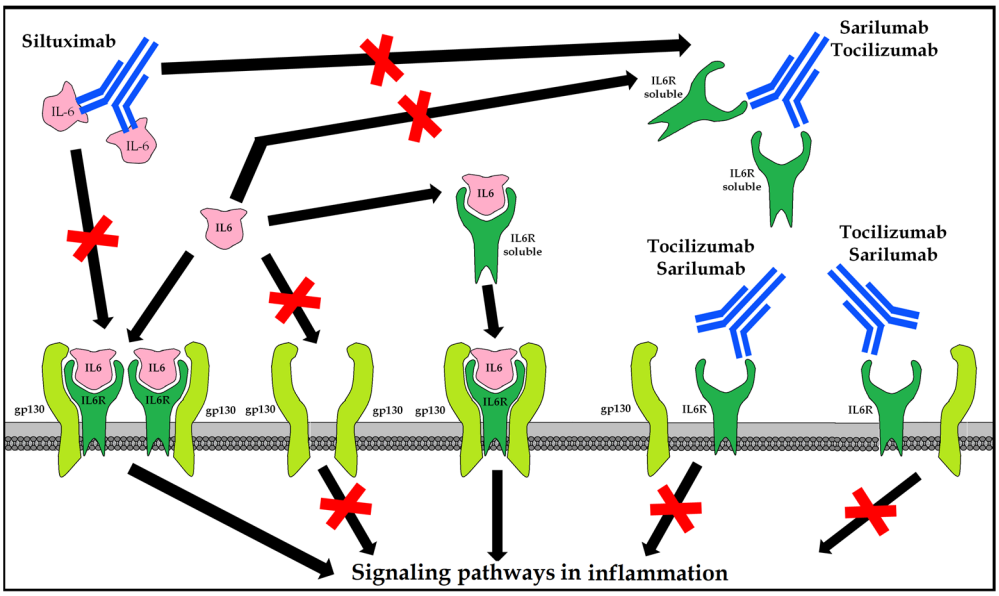

Figure 7. Therapeutic options for blocking the hyperinflammatory response mediated by IL-6.

10.6. Colchicine

The most studied pharmacological mechanism is the binding to tubulin, blocking the polymerization of microtubules, achieving an antimitotic effect [94,95]. It inhibits chemotaxis in phagocytosis in urate crystals in gouty arthritis [96]. The COLCORONA (Colchicine Coronavirus SARS-CoV-2) clinical trial (NCT04322682) studies the effect of colchicine on the inhibition of IL-1 production in COVID-19 [97].

10.7. Interferons

IFNs are divided into the following: type I (IFNα, IFNβ, IFN-ε, IFN-κ, and IFN-ω) [98], type II (IFNγ), and type III (λ). These have an antiviral effect, although types I and II induce the production of proinflammatory cytokines [99]. IFNα and IFNβ could be useful in early stages but would worsen survival in advanced stages.

Emapalumab (Gamifan®) is an anti-IFNγ mAb indicated for hyperinflammation in primary hemophagocytic lymphohistiocytosis (pHLH) [100] that has been tested in critically ill patients with COVID-19, as IFNγ levels are elevated in patients with COVID-19.

IFNλ has a powerful antiviral effect without a proinflammatory effect, so it could be a therapeutic option [101]. The antiviral role of pegylated IFNλ against HCV has been studied. Azithromycin inefficiently stimulates IFNλ production, which could explain its effect on COVID-19.

10.8. Passive Immunity

10.8.1. Sera from Patients Recovered from COVID-19

It was previously used in epidemics of the H1N1 influenza virus [102–104], SARS-CoV-1, and MERS-CoV [105,106]. The appearance of new mutant variants of SARS-CoV-2, such as Delta or Ómicron, which are increasingly contagious and escaped the neutralizing

antibodies of previous variants and vaccination (active immunization), has produced successive waves of epidemics [106].

10.8.2. Combined Immunoglobulin Preparations

In the future, and similarly to human anticytomegalovirus immunoglobulin (CMVIG, Megalotect®) (cytomegalovirus immune globulin), commercial preparation of immunoglobulins from different donors would be a therapeutic option, providing a higher concentration than plasma from recovered subjects.

10.8.3. mAbs Directed against Any SARS-CoV-2 Protein

Analogous to palivizumab against respiratory syncytial virus (RSV) [107], the design of an mAb directed against SARS-CoV-2 could be a therapeutic option applied to any infection. Bebtelovimab (LY-CoV1404, 1404) [108] is a neutralizing mAb directed against the S protein of SARS-CoV-2, including Ómicron. Tixagevimab and Cilgavimab (AZD7442) are mAbs isolated from B lymphocytes from patients infected with SARS-CoV-2 that neutralize protein S [109].

10.9. Active Immunity

In the race to manufacture the anti-SARS-CoV-2 vaccine [19], there are more than 125 anti-SARS-CoV-2 vaccine candidates [20]. They are divided into six large groups: (a) live attenuated viruses, inactivated viruses, nucleic acids, replicating viral vectors, non-replicating viral vectors, and recombinant protein subunits. There are studies on the immunomodulation achieved with the bacillus Calmette–Guérin (BCG) vaccine [110].

Some of the vaccines based on RNA technology that express part of the SARS-CoV-2 S protein in host cells are as follows: BNT162b2 (Comirnaty®, Pfizer-BioNTech, Mainz, Germany) [111] and mRNA-1273 (Moderna, Cambridge, MA, USA) [112]. As RNA is more easily degraded than DNA, DNA-based vaccines have also been marketed: ChAdOx1/AZD1222 (Oxford University/Astra Zeneca, Cambridge, UK), which uses a similar mechanism but is based on a chimpanzee adenovirus viral vector, as well as Ad26.COV2.S [113] (Janssen, Beerse, Belgium), carrying a non-replicating adenovirus serotype 26 viral vector with SARS-CoV-2 protein S genes.

11. Conclusions

Although efficacy and safety studies in humans are needed, the possible therapeutic targets in the viral response phase and in the hyperinflammatory response phase of COVID-19 have been reviewed. There is no current evidence to recommend any specific treatment. The use of investigational drugs must be carried out under controlled, randomized, and ethically controlled trials. Passive immunity studies have been carried out through the transfusion of plasma from recovered subjects; even so, there is a race to develop a vaccine that generates active immunity.

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Abbreviations

mAb	monoclonal antibody
RNA	ribonucleic acid
COVID-19	coronavirus disease 2019 (coronavirus disease-2019)
CQ	chloroquine
ACE2	angiotensin-converting enzyme type II
ERGI	intermediate compartment endoplasmic reticulum–Golgi apparatus
HCoV	human coronavirus
HCQ	hydroxychloroquine
IFN	interferon
IL-1	interleukin 1 (interleukin 1)
IL-6	interleukin 6 (interleukin 6)
IMPα/β1	importin alpha and beta-1
PI	protease inhibitor
JAK	Janus kinase (Janus kinase)
MERS-CoV	virus causing Middle East respiratory syndrome (Middle East respiratory syndrome coronavirus)
NS3	nonstructural protein 3
RdRp	RNA-polymerase-RNA-dependent
RDV	remdesivir
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1 (severe acute respiratory syndrome coronavirus 1)
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2 (severe acute respiratory syndrome coronavirus 2)
TMPRSS2	transmembrane protease, serine 2
HCV	hepatitis C virus
HIV	human immunodeficiency virus
RSV	respiratory syncytial virus

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