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Pharmacological approach and therapeutic options for SARS-Cov-2 infection. Fast update.

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Abstract

In these months the diffusion of a novel human RNA betacoronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is causing a worldwide public health emergency, originated in Wuhan, China. The disease caused by this new coronavirus, called "COVID-19", is very contagious and, although most of infected subjects are asymptomatic or have mild flu-like symptoms, the rapid spread of the virus has resulted in a significant amount of serious interstitial pneumonia that may quickly develop into severe acute respiratory distress syndrome (ARDS), septic shock, sepsis-induced coagulopathy and fatal multiorgan dysfunction. Hence, the unabated spread of the disease demands an immediate need to explore all the plausible therapeutic and prophylactic strategies for reducing the high morbidity and mortality of this infection. At present, there is no vaccine or certainly effective antiviral treatment for human SARS-Cov-2 and the mainstay of clinical management is prevalently symptomatic treatment combined with therapy based on a panel of drugs having variable and uncertain efficacy. Unfortunately, no many drugs have yet been approved to treat human SARS-Cov-2 infection and many agents are administered in off label route; several options are being studied to control or prevent clinical manifestations of this infection, including monoclonal antibodies, antiviral and anti-cytokine agents, antibiotics, and other drugs.

The effort of this narrative review is to quickly summarize the main therapeutic agents that are currently employed in daily clinical practice for the drug treatment of COVID-19; moreover, purpose of this work is to provide “first-line” physicians a consultation tool to tackle this health emergency.

Keywords: SARS-CoV-2 infection; Pneumonia; COVID-19; Pharmacological therapy.

1. Introduction

In these months the diffusion of a novel human RNA betacoronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is causing a worldwide public health emergency, originated in Wuhan, China. The disease caused by this new coronavirus is commonly called "COVID-19", which is the acronym of "coronavirus disease 2019" [1].

SARS-Cov-2 is very contagious and its rapid propagation has spread globally; there are three main transmission routes of COVID-19 infection: droplets, contact and aerosol transmission [2]. The gold standard for diagnosis of SARS-Cov-2 infection is real-time polymerase chain reaction fluorescence (RT-PCR) to detect SARS-CoV-2 nucleic acid in samples of sputum or throat swab and in secretions of upper respiratory tract. Other potential diagnostic method might be the detection of specific IgM and IgG antibodies against SARS-Cov-2 in blood samples, although this method seems more appropriate for population screening [3]; in a recent study, the median duration of IgM anti-SARS-Cov-2 antibodies detection were 5 days, while IgG were detected on 14 days after symptom onset [4], then humoral immune response to SARS-CoV-2 might aid in the diagnosis of infection, including subclinical cases.

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Although most of infected subjects by SARS-Cov-2 are asymptomatic or have mild flu-like symptoms, such as fever, cough, arthromyalgias and fatigue [5], but also diarrhea, ageusia and anosmia [6,7] , the rapid spread of the virus has resulted in a significant amount of serious interstitial pneumonia that may quickly develop into severe acute respiratory distress syndrome (ARDS), septic shock and fatal multiorgan dysfunction that are the most severe clinical manifestations of Sars-Cov-2 infection. Acute pulmonary embolism and disseminated intravascular coagulation, so called "sepsis-induced coagulopathy" [8], may complicate pneumonia, then these complications must be also considered in patients with sudden worsening of hypoxaemia, respiratory distress and reduced blood pressure [8,9].

High serum levels of Interleukin-6 (IL-6) and D-Dimer seem closely related to the occurrence of severe COVID-19 and their combined detection may be very useful for early prediction of the severity of COVID-19 patients [10]. In severe cases, the patients present frequently with lymphopenia and neutrophilia, hypoalbuminemia, high serum levels of alanine aminotransferase, lactate dehydrogenase, C-reactive protein, ferritin, and sudden oxygenation deterioration [11]. Computed Tomography (CT) scan of the chest shows interstitial pneumonia as bilateral peripheral ground-glass opacities and presence of possible acute pulmonary embolism [12].

Asymptomatic and pre-symptomatic SARS-Cov-2 shedding posts a big challenge to infection control; in addition, patients with mild and unspecific symptoms are also difficult to identify and quarantine [13]. Hence, the unabated spread of COVID-19 demands an immediate need to explore all the plausible therapeutic and prophylactic strategies for reducing the high morbidity and mortality of this infection. At present, there is no vaccine or certainly effective antiviral treatment for human SARS-Cov-2 and the mainstay of clinical management is prevalently symptomatic treatment combined with therapy based on a panel of drugs having variable and uncertain efficacy; oxygen therapy, lung ventilation and life support in intensive care unit are necessary in seriously ill patients [14].

The effort of this short review is to quickly summarize the main therapeutic agents currently employed in daily clinical practice for the drug treatment of SARS-Cov-2 infection; moreover, purpose of this work is to provide "first-line" physicians a quick consultation tool to tackle this health emergency.

2. Pharmacological approach

Unfortunately, no many drugs have yet been approved to treat human SARS-Cov-2 infection. Several options are being studied to control or prevent clinical manifestations of the infection, including vaccines, monoclonal antibodies, antiviral and anti-cytokine agents, antibiotics, and other drugs.

Many studies and clinical trials have been started and are currently ongoing in all Countries affected by this severe pandemic. New interventions are likely to require months to years to develop but, given the urgency of this health emergency, the scientific community is making available to clinicians therapeutic experiences and field trial results carried out during these months. Originally, the therapeutic approach was to repurpose some drugs already used to treat two previous infections caused by other human coronaviruses as severe acute respiratory syndrome (SARS) [15] and Middle East respiratory syndrome (MERS) [16].

At the moment, a multitude of compounds are under investigation for the treatment of this emerging disease, but there is an urgent need for effective therapy to treat symptomatic patients and decrease virus carriage duration in order to limit the transmission in the community.

3. Drug treatment options

Among candidate drugs to treat COVID-19, repositioning of old drugs for use as antiviral treatment is an interesting strategy because knowledge on safety profile, side effects, posology and drug interactions are well known. Given the state of health emergency, taking advantage also from chinese experience data, in most affected Countries many drugs are administered in off label route.

In this update we will prevalently refer to drugs having more evidence of effectiveness in current Literature.

3.1. 4-Aminoquinolines

Chloroquine and its hydroxy-analog Hydroxychloroquine, two derivatives of 4-aminoquinoline, commonly used as antimalarial agents and for treating Rheumatoid Arthritis and related diseases, are showing efficacy in patients with SARS-Cov-2 infection [17-21]. Chloroquine and Hydroxychloroquine have been reported to have potential antiviral effect related to their ability to accumulate in lysosomes and autophagosomes of phagocytic cells, blocking virus infection by alkalising the endosomal environment; this property hampers the low-pH-dependent steps of viral replication, including fusion and uncoating, as well as the glycosylation of cellular receptors of SARS-CoV-2. These functions may negatively influence the virus-receptor binding, resulting in a potential effect on both entry and post-entry stages of the SARS CoV-2 infection [17,18].

4-Aminoquinolines are likely to attenuate the severe progression of COVID-19 inhibiting the so called "cytokine storm", particularly interleukin-1 (IL-1) and tumor necrosis factor-α (TNFα), by suppressing T cells activation [21,22]. In a recent in vitro study, based on pharmacokinetic models [23], Hydroxychloroquine was found to be 3-times more potent than Chloroquine. Hydroxychloroquine is also preferred because of its lower incidence of gastrointestinal adverse reactions and lower risk of retinopathy compared with Chloroquine; moreover, in subjects with glucose-6-phosphate dehydrogenase deficiency, Chloroquine might cause hemolytic anemia and, therefore, it would seem prudent not to use Chloroquine to treat COVID-19 patients who have this genetic condition [22,24].

Other potential side effects of 4-Aminoquinolines therapy are the risk of hypoglicaemia [25] and, mainly, cardiotoxicity [26] and potential QT prolongation [27]. 4-Aminoquinolines are not safe nor recommended in patients already in treatment with other drugs that may cause QT interval prolongation [28]. Glycaemic control, electrocardiogram monitoring, careful cardiac surveillance and visual exam might be necessary. Hydroxychloroquine elimination is predominantly (40-50%) via renal excretion [29].

An oral loading dose of 400 mg twice daily of Hydroxychloroquine, followed by a maintenance dose of 200 mg given twice daily for the next 4 days is one the most common options for initial management of SARS-CoV-2 infection and, particularly in the early stages, Hydroxychloroquine seems to attenuate the severe progression of COVID-19 [23, 30].

3.2. Macrolides

Macrolides represent a drug family of protein synthesis inhibitors, which act as bacteriostatic antibiotics, by binding to bacterial 50S ribosomal subunit and interfering with protein synthesis [31]. These antibacterial agents are active mainly against Gram-positive and atypical bacterial species commonly associated with respiratory tract infections; they are also active against various Mycoplasmas [32]. Clarithromycin and Azithromycin are commonly used in clinical practice and there is evidence regarding their potential anti-inflammatory and immune-modulatory effects [33-36].

Clinical studies have shown as Macrolides may attenuate extreme cytokine production and promote immunoglobulin induction reducing respiratory viral infections complications [37-39]. In some studies Macrolides have been administered in patients with different viral respiratory infections, including Influenza, but with controversial results [3, 38, 40, 41]. However, in other studies Azithromycin has been shown to be *in vitro* active against Zika and Ebola viruses and to prevent severe respiratory tract infections when administered in patients suffering viral infection [42-45].

It was recently suggested a potential synergistic effect by combinating Hydroxychloroquine and Azithromycin; in a small sample size study Hydroxychloroquine treatment resulted significantly associated with viral load reduction in COVID-19 patients and its effect was reinforced by Azithromycin [46]

Biliary excretion, predominantly unchanged, is a major elimination route of Azithromycin; its most common side effects are diarrhea, nausea, abdominal pain and vomiting. Because of potential hepatotoxicity, Azithromycin should be immediately discontinued so far as signs and symptoms of hepatic dysfunction occur. QT interval prolongation was reported in patients taking Azithromycin [31] and, as for 4-Aminoquinolines, electrocardiogram monitoring is recommended. Azithromycin is not safe nor recommended in patients already treated with other drugs that may prolong QT interval [28]; for this reason we consider unwary and unwise uncontrolled treatment with Azithromycin/Hydroxychloroquine combination. Oral Azithromycin may be considered to treat COVID-19 patients, at dosage of 500 mg daily for 5 days.

3.3. Monoclonal antibodies

In most severe case of COVID-19 infection it has been shown a massive release of pro-inflammatory mediators and cytokines, in particular Interleukin-6 (IL-6) and Interleukin-1 (IL-1), linked to viral replication and leading to cytokine release syndrome-like [47]. Given that IL-6 and IL-1 play a pivotal role in this hyperinflammatory condition, it has been suggested a potential role of their blocker agents as treatment option for SARS-CoV2 related interstitial pneumonia [48].

IL-6, a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts, is involved in several physiological processes, such as T-cell activation and immunoglobulin secretion, and is implicated in the pathogenesis of inflammatory diseases [49, 50]

Tocilizumab is a humanized anti-IL-6 receptor monoclonal antibody, able to inhibit IL-6-mediated signaling [51] and commonly used for subcutaneous therapy of rheumatoid arthritis at weekly dosage of 162 mg [52]; Tocilizumab is also used for treating other rheumatic diseases, as systemic juvenile idiopathic arthritis [53], and Giant Cell Arteritis [54].

In a small recent study it has been shown as intravenous administration of Tocilizumab improved pulmonary CT scan abnormalities and oxygen saturation and normalized C-reactive protein levels and lymphocytes count in most of the patients [55]. Based on these results, other clinical trials are currently ongoing in patients with Covid-19 pneumonia in many Countries. A phase III study (TOCIVID-19), based on intravenous Tocilizumab at dosage of 8 mg/kg repeatable after 12 hours, has been approved by the Italian Regulatory Drug Agency (AIFA) in 330 patients with COVID-19 pneumonia and early respiratory failure, setting 1-month mortality reduction as primary outcome [56].

Another Italian study is underway to evaluate the efficacy of early administration of Tocilizumab in patients with COVID-19 pneumonia [57].

Potential, but severe, side effects of Tocilizumab are liver enzyme abnormality and neutrophil and platelet count decrease; diverticular perforation in patient with colonic diverticular disease was described. Mild renal impairment does not impact pharmacokinetics of Tocilizumab [51].

At the moment there is poor but promising evidence concerning the efficacy of Tocilizumab, alone or in association with other agents, in treating COVID-19; pending the results of the ongoing studies, the treatment should be reserved, in authorized centers, prevalently for critically ill.

3.4. Antiviral agents

The need to urgently identify an effective therapy against SARS-Cov-2 led to explore antiviral drug strategies. The similarity between SARS-CoV-2 and other Betacoronavirus associated with previous epidemics suggests to attempt treatment procedures involving drugs already used in previous viral infections [58]. Based on data from chinese and korean therapeutic experiences, treatment with Lopinavir/Ritonavir co-administration is, at the moment, one of antiviral therapy most included in majority of COVID-19 treatment protocols [59-62].

Lopinavir/Ritonavir co-administration is currently used for treating HIV-1 infected patients; both active substances have protease inhibitor activity and block viral protease involved in replication mechanisms. Lopinavir provides the antiviral activity while Ritonavir mainly works as a 'booster' to slow down the rate of Lopinavir metabolism in the liver. In HIV-1 infected patients Lopinavir and Ritonavir are orally co-administered once or twice daily, at dosage of 400mg and 100 mg respectively. Potential common side effects of the treatment are cold, nausea and diarrhea; rare case of pancreatitis, osteonecrosis, P-R interval prolongation and atrioventricular blocks were reported in patients taking Lopinavir/Ritonavir. Potential interferences with drug metabolism of other agents broken down by cytochrome p4503A (CYP3A) should be considered. Renal clearance of Lopinavir and Ritonavir is negligible while these drugs must not be used in patients with severe liver disease [63].

In patients with SARS-Cov-2 pneumonia, Lopinavir and Ritonavir were prevalently co-administrated, twice daily, at oral dosage of 400 mg and 100 mg respectively, for two weeks. Despite the evidence of Lopinavir/Ritonavir ability in reducing viral load and in improving disease outcome [60], there are controversial results regarding clinical improvement and reduced mortality in COVID-19 pneumonia [61,64]. These early data should stimulate immediate further studies to evaluate these drugs and other antiviral agents in the treatment of SARS-CoV-2 infection; in particular, it should be assessed whether combining Lopinavir/Ritonavir with other antiviral agents, as has been done in SARS [65,66] and in MERS [67], might enhance antiviral effects and improve clinical outcomes. At the moment, a number of other antiviral agents are advancing in clinical studies [68].

3.5. Anticoagulant treatment

Due to septic state [69], coagulopathy is a potential serious complication of SARS-Cov-2 pneumonia and this event is associated with poor prognosis [70-72]. Occlusion and microthrombosis formation in small pulmonary vessels of critical patient with COVID-19 have been reported in the majority of deaths [73].

For improving outcome, early administration of Heparin in COVID-19 patients has been suggested by an expert consensus in China [74], due to the risk of disseminated intravascular coagulation and venous thromboembolism [75,76].

Venous thromboembolism risk in patients with severe COVID-19 needs to be assessed, and effective prophylactic measures should be carried out for high-risk patients. Low molecular weight heparin, which has also anti-inflammatory effect [77], such as subcutaneous Enoxaparin 4.000-6.000 UI daily, for 7 days or longer, is advisable. In patients with documented pulmonary thromboembolism, treatment with low molecular weight heparin at therapeutic doses, or with subcutaneous Fondaparinux 7.5 mg daily, imbricated with Direct Oral Anticoagulants (DOACs), must be started [78].

Disseminated intravascular coagulation may complicate SARS-Cov-2 pneumonia [79] and, as the septic shock, is one of the major causes of multiorgan dysfunction [80]. In severe and advanced stages of Covid-19 pneumonia, diagnostic criteria for Disseminated intravascular coagulation must be implemented [81-83] and, in addition, it is advisable to use specific criteria for Sepsis-induced coagulopathy (SIC score), based on platelet count, prothrombin time ratio and Sequential Organ Failure Assessment (SOFA) [84]. Some studies suggest that septic patients might just benefit from early recognition and specific anticoagulant treatment [85, 86]. Based on recent evidence [87], in Covid-19 pneumonia only selected patients meeting SIC criteria or with markedly elevated D-dimer may benefit from therapy with Low molecular weight heparin.

3.6. Corticosteroids

Corticosteroids efficacy in rapidly suppressing inflammation is well known, but their adverse events, particularly severe infections and high risk to develop comorbidities further increasing infection risk, represent a serious limiting factor. Although Corticosteroids suppress the host inflammatory response, which in case of viral respiratory infections is the major responsible for lung damage, these drugs may delay viral clearance by inhibiting the immune response [88-90].

There is controversial evidence in results from studies that evaluated, in different infectious diseases, potential correlations between Corticosteroid treatment and some outcomes such as mortality, bacterial and fungal co-infections, and, above all, emergence of antiviral resistance in influenza-associated pneumonia or ARDS [91,92], delay in MERS-CoV RNA clearance [93] and increased viral load in SARS patients [94] or in respiratory syncytial virus-related illness [95]. However, recent data from meta-analysis reported in flu patients receiving Corticosteroids increased mortality, increased rate of secondary bacterial or fungal infection and longer stay in intensive care unit [96]. Moreover, a recent Cochrane Systematic Review concludes that there is insufficient evidence to recommend Corticosteroids in ARDS treatment [97].

Overall, no clear reason exists to expect that patients with COVID-19 infection will benefit from Corticosteroids and they might be more likely to be harmed with such therapy [98]. In the treatment of COVID-19 infection, current evidence advises against the use of these drugs unless indicated for another reason. Recent World Health Organization (WHO) guidance [99] recommends that Corticosteroids should not be used in 2019-nCoV-induced lung injury or shock, except in setting of clinical trial. However, chinese clinical experiences suggest that benefits and harms should be carefully weighed before using Corticosteroids. Based on existing studies and clinical experience, despite there is no significant improvement in overall survival, Corticosteroids might be used prudently in critically ill patients with 2019-nCoV pneumonia; dosage should be low to moderate (≤ 0,5–1 mg/kg daily of Methylprednisolone or equivalent) and treatment duration should be no more than 7 days [100]. Of course, optimal treatment strategy should require constant adjustment as patient's clinical performance changes; adverse drug reaction monitoring is imperative.

At the moment, there is agreement on avoiding early or long-term administration and high dosage of Corticosteroids given that these drugs might delay viral clearance and increase mortality risk; as for the rest, the use of Corticosteroids is yet controversial in Covid-19 patients and "to use or not to use" remains a therapeutic dilemma. There is a need for well designed and randomised controlled trials to promote more solid foundation for treatment recommendations.

3.7. Antibiotics

It is well known as co-infections with bacterial pathogens often occur in respiratory viral infections [101] and standard infection control and prevention techniques should be implemented, particularly into intensive care unit.

Although recent clinical practice guidelines recommend standard antibacterial therapy for adults with confirmed influenza and community-acquired pneumonia [102], at the moment there are not position statement nor guidelines regarding a potential antibiotic prophylaxis or empiric antibacterial therapy in Covid-19 infected patients. Apart from Azithromycin, treatments with Quinolone antibiotics and Cephalosporins result from few available data of chinese clinical experience [103].

Based on previously evidence, Teicoplanin [104], a glycopeptide antibiotic routinely used to treat staphylococcal and other Gram-positive bacterial infections, might be preferred for antibacterial treatment in Covid-19 patients. Teicoplanin was found to be active in vitro against SARSCoV and has joined the list of molecules that could be used in the therapeutic arsenal against COVID-19 [105]. This antibiotic already showed efficacy against viruses as Ebola, influenza virus, flavivirus, hepatitis C virus and human immunodeficiency virus (HIV), as well as against coronaviruses such as Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV [106-108]. Teicoplanin acts on an early stage of viral life cycle and the antibiotic concentration required to inhibit 50% of viruses (IC50) in vitro seems to be much lower than the concentration reached in human blood during usual administration (8.78 μM for a daily dose of 400 mg) [105]. Although these preliminary results need to be confirmed in randomised clinical trials, Teicoplanin, as Macrolides, might represent an antibacterial of choice in Covid-19 patients requiring antibiotic treatment [109]. Apart from potential ototoxicity, Teicoplanin is fairly well tolerated and has a sufficient safety profile. Cases of thrombocytopenia have been reported with Teicoplanin, then periodic haematological controls are recommended during treatment; since Teicoplanin is mainly excreted by the kidney, drug dose must be adapted in patients with renal impairment.

However, in COVID-19 patients we reiterate that bacterial culture tests and antibiogram have to drive antibiotic therapy.

3.8. Vitamin supplements

There is evidence that patients with acute infections have low circulating levels of Vitamin C levels, due prevalently to metabolic consumption [110,111] and several experimental and clinical studies have proved antimicrobial properties and antiviral effects of Vitamin C [112-115].

It has been shown, in vitro and in vivo, that Vitamin C might reduce the risk of infections and has immunomodulatory functions, particularly in high concentrations and in form of dehydroascorbic acid [113,114,116-120]. Vitamin C may have beneficial effects in patients with viral infections by increasing α/β interferon production and downregulating pro-inflammatory cytokines production [121,122]. Additionally, Vitamin C is a powerful antioxidant compound directed against free radicals and reactive oxygen species [123,124]. There is evidence that Vitamin C infusion may improve sepsis and sepsis-induced multiorgan dysfunction [113] and reduce mortality in patients with sepsis and severe acute respiratory failure [112]; improvement of lung inflammation induced by influenza A virus/H1N1 was also reported [125]. Results from other larger trials are awaited and further data on severe respiratory viral infection are needed.

Fruit and vegetables as citrus fruits, kiwi, mango, strawberries, papaya, tomatoes, green leafy vegetables, and broccoli are natural sources of Vitamin C [124] and recommended daily allowance (RDA) of Vitamin C is 75 and 90 mg for women and men respectively [124,126,127]; additional supplement of 35 mg daily is suggested in smokers, given that these subjects have lower Vitamin C status than nonsmokers [124]. Other evidence indicates that the RDA for Vitamin C could be too low and suggests that 200 mg daily is the optimum intake of Vitamin C for adult population, particularly during stress conditions [128].

Vitamin C is generally safe and well tolerated, even in large doses; gastrointestinal disturbances were observed in some individuals taking Vitamin C at dosage higher than 2 g daily and increased risk of kidney stones was also reported, due to high amounts of Vitamin C intake [124]. Despite there is no sure evidence on benefit of Vitamin C in patients with SARS-Cov-2 infection, nutritional supplementation is advisable; Vitamin C infusion should be evaluated in hospitalized patients.

It is well known that Vitamin D receptors are expressed on immune cells, as B cells, T cells, and antigen-presenting cells and it has been proved as Vitamin D has the capability to modulate innate and adaptive immune responses; moreover, there is evidence that Vitamin D deficiency is associated with increased susceptibility to common infections, like sepsis, pneumonia, influenza and other infectious diseases [129,130]. Data from a recent systematic review and meta-analysis

[131] regarding the effect of Vitamin D-calcium co-supplementation on inflammatory biomarkers confirm beneficial effect on plasma levels of C-reactive protein while such a beneficial effect was not observed for IL-6 and TNF-α concentrations.

Vitamin D is a fat-soluble vitamin naturally contained in very few foods (fatty fish, fish liver oils, beef liver, cheese and eggs) and available as a dietary supplement; it is also produced endogenously when ultraviolet rays from sunlight strike the skin. In nutritional supplements and fortified foods, Vitamin D is available in two forms, D2 (ergocalciferol) and D3 (cholecalciferol) and current RDA for Vitamin D is 600 IU daily for adults up to 70 years of age and 800 IU daily for those over 70 years [132].

We have not evidence regarding Vitamin D efficacy in COVID-19 patients, however, given that adult individuals are at increased risk to develop Vitamin D deficiency (serum levels <30 nmol/L), oral supplementation with prophylactic dosage of Vitamin D would not be inadvisable

3.9. Other agents

Several drugs, as Remdesivir [133], Ribavirin [134] and others, have shown efficacy to inhibit SARS-Cov-2 *in vitro* and have recently entered clinical trials.

In Italy, at the moment, apart from Tocilizumab clinical studies, AIFA approved two studies to evaluate efficacy and safety of Sarilumab, another IL-6 receptor antagonist authorized for treating Rheumatoid arthritis [135,136], Emapalumab, a monoclonal antibody against γ-interferon [137,138], and Anakinra, an IL-1 receptor antagonist [138,139].

4. Conclusion

SARS-CoV-2 infection is causing a worldwide public health emergency and several options are being studied to control and prevent clinical manifestations of this infection, including vaccines, monoclonal antibodies, antiviral and anti-cytokine agents, antibiotics and other drugs. Many studies and clinical trials have been started and are currently ongoing in all Countries involved in this severe pandemic. At the moment, several compounds are under investigation for the treatment of this emerging disease, but there is an urgent need for effective therapy to treat symptomatic patients and to decrease duration of virus carriage in order to limit the transmission in the community. Moreover, many studies might have several limitations, due prevalently to samples size relatively small and to short-term observation of the enrolled patients.

Based on previous therapeutic experiences, preliminary approach was to repurpose some drugs already used to treat other infections caused by human coronaviruses in the past, as SARS and MERS. Currently, pending stronger evidence of efficacy from ongoing trials, uncertainty remains about the most effective therapeutic approach and many drugs are administered in off label route. Probably, Hydroxychloroquine, alone or in controlled association with Azithromycin, seems to be the most reliable first-line strategy in terms of safety and feasibility. In more severe patients, Tocilizumab or Lopinavir/Ritonavir seem to be gaining more consensus. Therapy with low molecular weight Heparin should be started in selected patients, while the use of Corticosteroid is widely debated yet. Vitamin C supplements could be useful.

We hope scientific community will quickly conduct further research to provide effective and reliable therapeutic ways to manage this severe public health emergency in both the short-term and long-term.

Compliance with ethical standards

Disclosure of conflict of interest

The Authors declare no conflict of interest.

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