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Which Therapeutic Strategy for which Type of COVID 19 Patient?

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The continuing spread of SARS-CoV-2 remains a Public Health Emergency of International Concern. World Health Organization (WHO) reported, globally, the number of new weekly cases (21 to 27 November 2022) was just fewer than 2.7 million new cases reported and the number of new weekly deaths with about 8400 fatalities. And, as of 27 November 2022, 637 million confirmed cases and 6.6 million deaths have been reported globally. Three types of COVID 19 patients are distinguished from the French study, (i) patients with few clinical signs but with a high nasal viral load and being highly contagious; (ii) patients with mild symptoms at the beginning but worsening towards the tenth day with the appearance of a severe acute respiratory syndrome despite a decreasing viral load; (iii) patients with a rapid worsening to an acute respiratory syndrome with persistence of a high viral load in the nose and throat and appearance of SARS-CoV-2 blood viremia causing multivisceral failure leading to death [1]. The major clinical manifestations linked to COVID 19 are numerous and diverse, among which there are digestive disorders, coagulation disorders, acute respiratory distress syndrome, macrophagic activation syndrome, myocarditis linked to SARS COV2, acute tubulopathy linked to SARS COV2, meningoencephalitis linked to SARS COV 2. These can be explained by the fact that the cellular tropism of SARS COV 2 is numerous as well as the physiopathogenic consequences. It concerns all cells with an angiotensin-converting enzyme 2 (ACE 2) receptor (example, alveolar epithelial type II cells, upper and stratified epithelial cells of the esophagus, absorbent enterocytes of the ileum and colon, pancreatic cells, glial cells, Sertoli cells) [2]. The interactions between SARS COV 2 and ACE2 cells lead to their internalization and massive viral replication with cellular damage, activation of the inflammatory process, activation of the immunological system, stimulation of the coagulation system, among others [2]. The various physiopathogenic consequences during COVID 19 largely explain its numerous therapeutic targets. What physicians need to know about physiopthothogeny with identified therapeutic targets, holistic diagnostic and therapeutic approach of Covid-19 is the subject of ongoing updates from experts at this Journal.

Early diagnosis and management of COVID 19 improves prognosis. During the onset manifestation, the most common symptoms were fever (98%), cough (76%) and myalgia or fatigue (44%); less frequent symptoms were sputum production (28%), headache (8%), hemoptysis (5%) and diarrhea (3%) and more than half of the patients developed dyspnea [3]. At this stage, primary viral replication followed by cellular damage is presumed to occur in the mucous epithelium of the upper respiratory tract (nasal cavity and pharynx), with additional multiplication in the lower respiratory tract and the gastro-intestinal mucosa [4]. Activation of the immune system, which follows, is important. If this immunological response is adequate, the infection can be controlled and the patient remains asymptomatic. In contrast, it has been shown that SARS CoV 2 can block this antiviral immunity early, effectively and durably in the most serious cases [5]. Anticoronavirals should be helpful during this stage. It should be remdesivir (by antiviral activity against SARS-CoV-2), ritonavir boosted nirmatrelvir (SARS-CoV-2 main protease inhibitor and an HIV-1 protease inhibitor and CYP3A inhibitor), chloroquine and its derivative hydroxychloroquine (by a modification of an attachment protein on the head of the virus), baricitinib (by inhibiting cyclin G), among others. After this stage, major manifestations could be occurred.

Major clinical manifestations linked to COVID 19 include digestive disorders, coagulation disorders, acute respiratory distress syndrome (ARDS), macrophagic activation syndrome, etc. These imply specific therapeutic approaches over anticoronaviral therapy.

Digestive disorders

The digestive manifestations during COVID 19 are various: anorexia (83.8%), diarrhea (29.3%), vomiting (0.8%) and abdominal pain (0.4%) [6]. The interaction between SARS COV2 and intestinal microbiota on the one hand resulting a modification of microbiota, thus favoring the appearance of the cytokine storm and on the other hand interaction between SARS COV 2 and intestinal cells leads to their destruction [6]. Therefore, one of the therapeutic targets would be to add commensal bacteria to improve this modification. Another would also be to manage the cytokine storm. Some biological Disease-Modifying Antirheumatic Drugs (bDMARD) and targeted synthetic Disease-Modifying Antirheumatic Drugs (tsDMARDs) have given encouraging results in the cytokine storm management.

Coagulation disorders

It manifests as thrombosis of small pulmonary vessels, pulmonary embolism, thrombosis of small skin vessels, deep vein thrombosis, hemorrhage of small vessels, disseminated intravascular circulation (DIC), etc. Activation of the coagulation system and fibrinolytic system result from systemic inflammation, endothelial dysfunction by interaction with SARS COV 2, severe hypoxemia and the production of antiphospholipid antibodies leading to clot formation. Anticoagulants are therefore essential in the management of these coagulation disorders. Heparin and direct oral anticoagulants can be used [7].

Acute respiratory distress syndrome (ARDS)

It is characterized by acute onset of respiratory distress maked by dyspnea with hypoxia and hypocapnia; tachypnea; intercostal, sub sternal, supernal, supraclavicular pulling; crackling rales etc. The interaction between SARS COV 2 and red blood cells leads to a decrease in the capacity of hemoglobin to transport and efficiently exchange CO2 and O2 through the alveolo-capillary barrier which in the long term causes an alteration of the alveolo-capillary barrier, then can progress to pulmonary fibrosis. In addition, the interaction between SARS COV 2 and alveolar epithelial type II cells leads to the destruction of alveolar epithelial type II cells with production of hyaline membrane plus the alveolo-capillary barrier damage [2, 8]. A treatment based on hydroxychloroquine (by its action on the preservation of hemoglobin) allows to maintain the normal transport of oxygen (O2) and carbon dioxide (CO2) through the alveolo-capillary membrane. Certain bDMARDs can be used such as interleukin-6 (IL-6) blocker that seems to hold great promise for managing the massive cytokine storm associated with the development of typical lung damage and ARDS). tsDMARD can be also used (by interference with Janus kinase) in its management. Corticosteroids reduce excessive and harmful pulmonary inflammation, but they also inhibit the beneficial immune response which allows the patient to eliminate pathogens.

Macrophagic activation syndrome

It manifests clinically by high fever, hepatosplenomegaly, lymphadenopathy among others and biologically by hyperferritinemia, hypofibrinogemia, pancytopenia, hepatocellular insufficiency etc. The interaction between SARS COV2 and cells having ACE 2 receptor induces an activation of the inflammatory process: vasodilation, vascular hyperpermeability, infiltration of inflammatory cells leading to the release of pyrogenic cytokines or even a cytokine storm (interleukin-6, interleukin-8, interleukin-10, tumor necrosis factor, etc) [2]. Therapies targeting the pro-inflammatory cytokines can improve macrophagic activation syndrome. Corticosteroid therapy and certain bDMARDS such as Anakinra (interleukin 1 receptor antagonist) have been discussed in management.

So, what therapeutic strategy? The complexity of its pathophysiology, the multiple therapeutic targets and the absence of effective anticoronaviral monotherapy proven at the current state of knowledge are arguments to say that it is necessary to consider blocking several therapeutic targets in order to increase the anticoronaviral effectiveness. Hence the need to combine anticoronaviral therapeutic means taking into account the type of COVID 19 patient and in particular all the major clinical manifestations linked to COVID 19.

Anticoronaviral multitherapy proposed by some authors may be the solution, if and only if, it can suppress viral replication and prevent the immune system from dysregulation. Indeed, clinical trial is underway to assess the efficacy and tolerance of the triple-drug therapy combining baricitinib, lopinavir / ritonavir and remdesivir [9]. The genetic susceptibility of COVID 19 patients to develop the severe form is not yet well established. Could anticoronaviral multitherapy prevent progression towards severe form? However, it has been shown that a reduced viremia does not prevent the immune system from racing and its progression towards the severe form [1]. Suppressing the virus does not seem to be enough. It would be better that all the management strategies are focused on the early diagnosis and adequate treatment of the type of COVID 19 patient and in particular all the major clinical manifestations linked to COVID 19. Anecdotally, we will say that no drug proposed is effective, all the drugs proposed are effective, it is a question of early diagnosis and adequate treatment of the types of patient and all the major clinical manifestations linked to COVID 19.

This information will help to develop therapeutic strategies depending on the type of COVID 19 patient and in particular all the major clinical manifestations linked to COVID 19 instead to continuing to take account only an anticoronaviral monotherapy or anticoronaviral multitherapy, knowing well that the immune system dysregulation with its inflammatory corollary persists despite the decrease of viremia.

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