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ORIGINAL ARTICLE
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Reasoned therapeutic protocol in outpatients with COVID-19

Claudio ALLEGRA [1], Giacomo FAILLA [2] *, Luca COSTANZO [2], Ferdinando MANNELLO [3], Francesco MONTELLA [4], Pier L. ANTIGNANI [5]

[1]Department of Angiology, Union Internationale de Phlebologie (UIP), S.Giovanni Hospital, Rome, Italy; [2]Unit of Angiology, Department of Cardiovascular Disease, San Marco Hospital, Rodolico - S. Marco University Hospital, University of Catania, Catania, Italy; [3]Unit of Clinical Biochemistry - Section of Biochemistry and Biotechnology, Department of Biomolecular Sciences, Carlo Bo University of Urbino, Urbino, Pesaro-Urbino, Italy; [4]Department of Internal Medicine, San Giovanni-Addolorata Hospital, Rome, Italy; [5]Vascular Center, Nuova Villa Claudia, Rome, Italy

*Corresponding author: Giacomo Failla, Unit of Angiology, Department of Cardiovascular Disease, San Marco Hospital, Rodolico - S. Marco University Hospital, University of Catania, Catania, Italy. E-mail: jacomienko@gmail.com

ABSTRACT

Background: Seventy percent of patients affected by SARS-COV-2 disease are asymptomatic or with symptoms that not required Hospitalization. A prodromal period lasting about 5 days can be identified. In this phase a patient with a positive swab for viral RNA may or may not evolve towards the phase of symptomatic disease.

Methods: In this paper we reviewed the literature related to COVID-19 therapy we propose a reasoned treatment protocols in outpatients according to the age and the comorbidity.

Results: The aim of this study was to reduce the impact of the virus by reducing its ability to attack cells and the inflammatory burden and the prothrombotic effects proposing two therapeutic schemes of proven efficacy according to the age of the patients and the comorbidities.

Conclusions: We aimed to reduce worsening of clinical status and hospitalization while protecting patients at home.

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Key words: COVID-19; Therapeutics; Blood coagulation disorders; Heparin, low-molecular-weight; Thrombosis.

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Seventy percent of patients affected by SARS-COV-2 disease are asymptomatic or with symptoms that not required Hospitalization. A prodromal period lasting about 5 days can be identified. In this phase a patient with a positive swab for viral RNA may or may not evolve towards the phase of symptomatic disease.

Materials and methods

The report produced by the Italian Higher Institute of Health on May, 07 2020 provides the following data (27.955 patients): 1) average age of death for COVID-19 patients is 81 years old; 2) 42.2% of deaths is in the age group between 80-89 years old; 3) 32.4% it is between 70-79 years; 4) 8.4% it is between 60-69 years; 5) 2.8% it is between 50-59 years; and 6) 14.1% it is over 90 years old.

The clinical status was only available in 4535 cases:

- asymptomatic 9%;
- mildly symptomatic 6%;
- symptomatic without specificity of gravity 16%;
- with mild non-specific symptoms 43%;
- with severe symptoms that required hospitalization 21;
- with critical gravity that required intensive care 5%.

The comorbidities were: 1) 3.9% of the sample showed no pathologies; 2) 15.0% showed 1 pathology; 3) 21.3% showed two pathologies; and 4) 59.9% showed three or more pathologies.

In the report of the ministry of health (update 2020, September 2) concerning the week from 19 to 23 August 2020 compared to the data of the month of May, there is a strong lowering of the median age of the population that contracts the infection, which in the last week stood at 29 years, with more and more frequent involvement of the younger age groups, as a consequence of the resumption of commercial activities and those related to recreational activities linked to summer holidays. Clinically, this has resulted in a lower clinical severity of diagnosed cases which, in most cases, are asymptomatic. On the other hand, there was a slight decrease in the number of symptomatic cases contracted locally and diagnosed in Europe.

Hypertension was the most represented comorbidity (74.6% of cases), coronary artery disease in 70.4% of cases, diabetes in 33.8% of cases.

Gender: male in 60.4% of cases.

In women (N.= 850) the average number of pathologies observed is 3.4 (median 3, standard deviation 1.9); in men (N.= 1771) the average number of pathologies observed is 3.2 (median 3, standard deviation 1.9).

The average time from the onset of symptoms to the hospitalization (sore throat, rhinorrhea cough and asthenia) was 5 days.[1]

Results

From these data we can deduce: 1) we are dealing with a predominantly elderly population, therefore carriers of fragility syndrome;[1, 2] 2) high prevalence of comorbidities; and third, the time to avoid direct (respiratory failure) and indirect (venous thrombosis and cytokine cascade) complications is 5 days from the beginning of non-specific symptoms.[1]

In order to avoid etiopathogenetic confusion and consequently therapeutic strategies, the following issue should be pointed out:

- etiological therapy, to suppress the causative agent of the disease;
- pathogenetic therapy, to interfere in the mechanisms of the disease onset;
- prophylactic therapy, to prevent the disease (vaccines and sanitation procedures);
- treatment of complication: complication is defined as an unfavorable evolution or consequence of a disease or therapy, or a new disease that appears as a consequence of a pre-existing disease or due to the presence of risk factors;
- treatment of comorbidities: comorbidity is defined as a disorder that occur temporally in conjunction with another disease, but are not caused by it.

These concepts are, in our opinion, necessary to clarify the real impact of viral infection.

Currently, in presence of COVID-19 (patients with positive swab for presence of viral RNA) in prodromal phase (asymptomatic, paucisymptomatic, symptomatic without specific gravity or with mild non-specific symptoms, about 70% of the population positive) we only have available competitive partial pathogenetic therapies on specific sites, therapies to prevent indirect complications related to the cytokine cascade, therapies to prevent or limit direct viral and saprophytic pulmonary complication and prophylaxis therapy for venous thrombosis.

A recent document from the "Istituto Superiore di Sanità" reports that in Italian patients, who died of COVID-19, during hospitalization antibiotic therapy was used less than antiviral therapy, more rarely steroid therapy (37%). 4.2% of SARS-CoV-2 infected patients received tocilizumab.[1]

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Competitive partial pathogenetic therapies on specific sites

Regarding pathogenetic therapies in the prodromal phase, we currently have few and incomplete research, all based on the concept of blocking some specific Coronavirus receptors to prevent acute respiratory distress[3] or to prevent the cellular entry of the virus SARS-CoV-2 by competitive action.[4]

Basically, even in competitive receptor pathogenetic therapies, inflammation occurs both as a process directly linked to the viral infection and as a self-maintaining process.

Therapies to prevent indirect complications related to the cytokine cascade.

Inflammation

From a pathophysiologic and biomolecular point of view, lung specimens from mild COVID-19 patients showed edema, proteinaceous exudate with globules, and patchy inflammatory cellular infiltration indicating that a marked inflammatory and immune responses may activate a "cytokine storm", and apoptosis of epithelial cells and endothelial cells; subsequently, vascular leakage, abnormal T cell and macrophages response may induce ARDS or even death.[5] Moreover, in the blood of patients with COVID-19, there was a marked increase in interleukin 1β (IL-1β), interferon γ (IFN-γ), interferon-inducible protein 10 (IP-10), and monocyte chemoattractant protein 1 (MCP-1), as well as IL-4 and IL-10 suggesting that in some COVID-19 patients, although being negative for the viral nucleic acid test, still sometimes present with a high level of inflammation.

Collectively, the finding indicates that inflammation is a major feature in COVID-19 patients. Thus, it has been hypothesized that excessive inflammation, depressed immune system, and an activate cytokine storm substantially contribute to the pathogenesis of COVID-19. In particular, in the early stages of coronaviruses infection, dendritic cells and epithelial cells are activated and express a cluster of proinflammatory cytokines and chemokines including IL-1β, IL-2, IL-6, IL-8, both IFN-α/ β, tumor necrosis factor (TNF), CeCmotif chemokine 3 (CCL3), CCL5, CCL2, and IP-10, etc. These are under the control of immune system. Thus, the overproduction of these cytokines and chemokines contributes to the development in disease. IL-10, produced by T-helper-2 (Th2), is antiviral, with an infection of coronaviruses leading to a marked decrease in this agent.[6]

Moreover, the amplification of the inflammatory response would promote cellular apoptosis or necrosis of the affected cells, which would further fuel inflammation, setting the basis of a deleterious vicious cycle, followed by increasing permeability of blood vessels and the aberrant accumulation of inflammatory monocytes, macrophages and neutrophils in the lung alveoli. This vicious circle would intensify the situation as the regulation of immune response is lost and cytokine storm is further activated, resulting in direct consequences.[5]

Discussion

These hypotheses are crucially supported by recent *in situ* studies highlighting the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. These findings suggest that SARS-CoV-2 infection facilitates the induction of endothelitis in several organs as a direct consequence of viral involvement and of the host inflammatory response. In addition, induction of apoptosis and pyroptosis might have an important role in endothelial cell injury in patients with COVID-19. In fact, COVID-19-endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19.[6]

All this evidence, hypothesis and *in-itinere* studies may provide a rationale for therapies to stabilize the endothelium while tack ling viral replication, particularly with anti-inflammatory, anticytokine.

Anti-inflammatory drugs: drugs with the aim of reducing inflammation, considered as the organism's response to prevent the persistence and spread of inflammation.

There are corticosteroid and non-steroidal anti-inflammatory drugs also called FANS. In COVID-19 inflammation it is preferable to use FANS drugs instead of corticosteroid in so called frail per age patients, because of the presence of one or more comorbidities that find contraindication on use of corticosteroids, as hypertension and diabetes and the strong immunosuppressive effect.

Among the different types of anti-inflammatory drugs, the use of hydroxychloroquine was preferred probably not only because of its anti-inflammatory effects by now consolidated in the care of connective diseases such as A.R,[7, 8] but also because of some of its features that distinguish it from glucocorticoids and from FANS, such as the increase of the pH within intracellular vacuoles and the alteration of the processes such as protein degradation by acid hydrolases in the lysosome, assembly of macromolecules in the endosomes and post-translation modification of proteins in the Golgi apparatus, and finally for controlling

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the cytokine storm that occurs late-phase in critically ill SARS-CoV-2 infection.[8]

In addition, the idrossichloroquine has demonstrated its efficacy in Chinese COVID-19 patients in clinical trials by reducing fever, improving CT imaging, and delaying disease progression, leading Chinese experts to recommend chloroquine-based treatment as a first line-treatment for mild, moderate and severe cases of COVID-19.[9]

The absence of an effective treatment against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has led clinicians to redirect drugs that are known to be effective for other medical conditions to the treatment of COVID-19. Key repurposed therapeutic agents among these are the antimalarial drug chloroquine and its analogue hydroxychloroquine, which is used for the treatment of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis[7] These drugs have been shown in laboratory conditions to have antiviral properties as well as immunomodulatory effects. However, the use of this class of drugs for COVID-19 is based on a small number of anecdotal experiences that have shown variable responses in uncontrolled observational analyses, and small, open-label, randomized trials that have largely been inconclusive.[8-11]

Therapies to prevent or limit direct viral and saprophytic pulmonary complication

In most severe cases SARS-CoV-2 pneumonia occurs with the presence of bilateral interstitial infiltrates and hypoxemia, defined as a critical decrease in the relationship between arterial PO_2 and FiO_2, configuring a clinical picture full blown of Adult Respiratory Distress Syndrome (ARDS). The patients with ARDS remain dependent on mechanical ventilation for a time varying between 10 and 14 days and show a high lethality.

To date, knowledge of the factors that influence the clinical severity of COVID-19 is limited and not unique.[12, 13]

Normally, in elderly patients, in case of diseases that may entail a bed or respiratory complication, antibiotic coverage is applied as support therapy. This pharmacologic prevention called "antibiotic coverage" was applied also in the COVID-19 disease, also because of its respiratory pathogenic specificity: the almost universally accepted drug was azithromycin. The combination of hydroxychloroquine with a second-generation macrolide, such as azithromycin (or clarithromycin), has also been advocated.[9]

In this regard the A.A. propose the alternative use of doxycycline, the first choice drug in Rickettsiosis, for the following reasons: 1) this tetracycline is also used as antimalarial prophylaxis in the same way as hydroxychloroquine, for the same reasons of pharmacological mechanism;[14] 2) for a certain degree of genetic homology between Rickettsie and the virus which is opening new horizons in the fight against the HIV;[15] 3) for the specific actions against obligate endocellular parasites;[13] 4) because the study methods and *in-vitro* culture of these microorganisms are similar to those used for the viruses;[16, 17] 5) for the high tolerability even in prolonged therapies of months;[18] 6) because the treatment with doxycycline in RMSF avoids the complication of a DIC, a complication also reported in COVID-19 disease;[19] and 7) for the anticoagulant effects.[20]

Prophylaxis therapy for venous thrombosis

Regardless of the specific topic of venous thrombosis for and from COVID-19, in elderly patients with comorbidity, in the case of bedridden patients or reduced mobility, normally low molecular weight heparin (LMWH) prophylaxis is carried out at different dosages, depending on the degree of risk; although it is used for inpatients IMPROVE score may help to identify outpatients who are at high risk for VTE.[21, 22] This is now a custom accepted by all and present on all the GLs that deal with this topic.[23, 24] For years now, preference has been given to the use of LMWH, also for its anti-inflammatory and anti-neoplastic characteristics, efficacy recognized also for doxycycline.[25]

Coagulation and viral infection

In viral infections, a decrease in platelet function, a reduced production or an increase in destruction have been documented. Thrombocytopenia is an event that can occur in both hemorrhagic and non-hemorrhagic viral infections. In most cases, the cause is the presence of autoimmune antibodies against platelets. Other mechanisms determine the greater adhesion and activation, with consequent consumption of the platelets; also, the presence of the virus in the bone marrow directly affects the megakaryocytes and therefore the production of the platelets. In SARS-CoV infection, thrombocytopenia caused by autoantibodies,[26-29] the presence of high levels of von Willebrand factor in the blood,[30] and activation of coagulation cascade with final generation of fibrin have been reported. In humans and mice, the detection of fibrin clots in the alveoli is a feature of SARS-CoV infection. The purpose of the coagulation response is, probably, to protect the host by sealing the alveoli, preventing edema and alveolar hemorrhages, limiting, however, the exchange of oxygen.[31, 32]

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Conclusions

As mentioned above we can affirm: 1) currently, there is no specific causal therapy for Coronavirus; 2) in the proposed cases, they are outpatients because they are asymptomatic or paucisymptomatic but without respiratory compromise; 3) the treatment at home for COVID-19 has the dual purpose of preventing the complications of this disease and avoids overloading the hospital health facilities that could preserve assistance for other pathologies such as cancer; and 4) a rational home therapeutic protocol can help doctors without overload the national health system.

The therapeutic protocol rationale is based on fighting inflammation by avoiding the consequences of the cytokine cascade, preventing vascular thrombosis, preventing bacteriological complications, especially at the respiratory level. Therefore, use of steroidal and non-steroidal anti-inflammatory drugs, antithrombotic prophylaxis according to the individual risk and effective antibiotic-therapy with broad spectrum antibiotics without significant side effects is advisable.

Regarding azithromycin or doxycillin, the choice is oriented towards giving priority to a more selective antibiotic at the organ level, in the specific respiratory case, such as azithromycin, or to an antibiotic with characteristics more similar to antivirals; however, it should be remembered that both act on the protein synthesis of bacteria. On the use of Azithromycin, specific antibiotic coverage at the respiratory level may be considered necessary; on the use of doxycillin, the need to prevent microthrombosis at the pulmonary alveolar level can be invoked. Therefore, two different ways to obtain the same result. Azithromycin is richer in current studies on its specific efficacy for COVID-19. For doxycillin, we are on a hypothetical rationale; however, both are drugs of absolute manageability.

On heparin prophylaxis, there are already proven International Guidelines on dosages according to the degree of severity. As for the use of anti-inflammatories, the choice is linked to the presence of comorbidities that contraindicate the use of steroid drugs such as diabetes, hypertension and age.

We can therefore propose two therapeutic paths:

• therapeutic protocol standard for patients positive to coronavirus in prodromal phase: 1) azithrimicyn (500 mg/die once a day for three days); 2) paracetamol (15 mg/kg every 6 hours, or 10 mg/kg at 4 hour intervals per os, if present with fever and/or polymyalgia or if not non-responding patients; 3) dexamethasone (6 mg/die per os, max for ten days); and 4) L.M.W.H.: prophylaxis dosage according to different risk level;

• therapeutic reasoned protocol for patients positive to coronavirus in prodromal phase: 1) idrossichloroquine (400 mg twice day the first day, followed by maintenance dose of 200 mg twice day for 4 days as for the SARS-CoV-2 infection); 2) doxycicline (100 mg twice day for 5 days); and 3) L.M.W.H. (prophylaxis dosage according to different risk level).

Clinical control by measuring vital parameter (*i.e.* body temperature, O_2 saturation) is mandatory and periodical (if feasible) laboratory parameter including platelets count, D-Dimer, Creatinine clearance. In case of clinical status deterioration pulmonary imaging is mandatory.

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