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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Mini Review

COVID-19 So Much to Know - What about Two Old Drugs?

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Received: February 03, 2021; **Published:** February 16, 2021

Abstract

Through the modern information-technology the Covid-19 pandemic can be watched in real time by anybody. An enormous scientific information is teleported in the four walls of any physician's home and office in an almost minute takt. Healthcare workers, doctors and nurses experienced how difficult it may be to filter the rapid cumulating information and adjusting it with daily praxis. Hospital physicians dealing with Covid-19 had to struggled at least with three intertwined, gradually changing phases: diagnosis, avoiding aerosolization and therapy - which got in the background of public observation because of the now ongoing politically dominated vaccination phase. However, Covid-19 is coined by two pathways - early viral replication and immune response syndrome which may lead into a cytokine storm syndrome the leading cause of death in this pandemic. Remdesivir which is indicated in the early phase has a modest effect on morbidity and very little on mortality. On contrary the anti-inflammatory drugs steroids and possibly colchicine, two old drugs seem to be gamechangers as direct therapies of SARS-CoV-2 infection.

Keywords: *Covid-19; Vaccination Phase; SARS-CoV-2; Remdesivir*

The Covid-19 pandemic is a unique experiment, which almost everybody at least in the western countries is watching through modern technology of information. For the first time in history these two phenomena - a worldwide flue like illness with devasting global consequences and the overwhelming efforts of the information industry reporting almost any detail of this pandemic (to be carried in almost every single household) merge to a cocktail making it extremely difficult even for professionals to keep up. Hospital physicians dealing with Covid-19 had to struggle at least with three intertwined, gradually changing phases. The first was diagnosis. Can we identify SARS-CoV-2 early enough to differentiate between influenza, common could and Covid-19. Avoid clusters in hospitals and other health care institutes which put patients at unexpected risk or which may even work as a platform for further infections moving to the community outside the hospital. Everybody watched the evolution of rtPCR tests (reverse transcriptase polymerase chain reaction) and the meaning of their cycle thresholds, antigen tests better and better performing in analytic and clinical sensitivities and specificities. Finally, antibodies helping to differentiate between diverse pulmonary diseases or ongoing SARS-Cov-2 induced chronic pulmonary inflammation while PCR and antigen test are negative. The second phase was dominated by the question how to deliver oxygen but avoiding aerosolization and which medication might work against Covid-19. A myriad of studies flooded diverse communication canals. While recognizing a relief of stress in ventilation therapies from simple oxygen delivery via high flow devices to mechanical ventilation a "battle" between antiviral and anti-inflammatory therapy developed on the horizon which seems to be won by several medications acting against inflammation and cytokine activation caused by SARS-CoV-2 infection. In the meantime, the third phase raised - vaccination - monitored now by everyone and even becoming highly political. So, between the diagnostic step and masterplans of vaccination direct treatment of Covid-19 moved a little bit in the background but a lot have been learned about virus-host biology and medical therapies.

Covid-19 disease seems to be driven by two different pathways. First, early virus replication, when strong enough, leading to acute respiratory distress (ARDS) and second, rather late in the course of infection, an immune response syndrome leading to tissue damage in severe cases ending in a multi inflammatory syndrome (MIS) eventually followed by multi organ failure.

With respect to antiviral therapy, the harvest of all the efforts in interventional studies coming up the last year seems to be modest. Practically, remdesivir stands alone and serves as first line therapy in severe Covid-19 patients dependent on oxygen but not requiring mechanical ventilation. However, there are some preliminary data, that anti-SARS-CoV-2 antibodies (bamlanivimab, casirivimab plus imdemivab) just at the beginning of the disease in an outpatient setting may have positive effects against disease progression.

However, surprising are the therapeutical intervention in the later phase of the disease, when it comes to an exaggerated immune reaction and anti-inflammatory response. Ironically, two medications used in rheumatoid arthritis an old well-known illness, may overtake the therapeutically field in Coivd-19.

Covid-19 is a heterogeneous disease displayed in a spectrum of asymptomatic patients through patients with severe critical illness hardly or not surviving intensive care medicine with all its high technical supportive care systems. During the "learning curve" of the pandemic it became obvious, that disease progression is markedly determined by cytokine release eventually sliding in a cytokine storm.

How do we anticipate or realize this pathology?

There are striking laboratory features of Covid-19 like disproportionate high ferritin and D-Dimer levels accompanied with cytopenia especially lymphocytopenia, a high neutrophil to lymphocyte ratio (NLR) and laboratory findings of disseminated intravascular coagulopathy (DIC). Several pro-inflammatory cytokines are partially very high: IL-1, IL-2, IL-6, IL-12, IL-18; IL-33, TNFa and interferon for example.

Typically, histopathological examinations of lymph nodes and spleen display depletion of lymphocytes but activation of macrophages and monocytes [1]. This may be the reason of frequently seen lymphocytopenia. Lymphocytopenia is also dominant in autopsy specimen of Covid-19 lungs, in contrast to it, macrophages and monocytes are overrepresented [1].

How does it come this cyto-pathologically and laboratory phenotype?

In the very early phase of immune reaction antigen presenting cells (APCs) present epitopes of the antigen to natural killer cells and cytotoxic DC8-pos T cells. At this point the innate and the adaptive immune system get activated producing large amounts of pro-inflammatory cytokines and chemokines [2,3]. If not balanced early enough by anti-inflammatory cytokines, apoptosis of APCs and sufficient viral clearance of infected cells this process may lead to a cytokine storm accompanied with multi inflammatory syndrome (MIS) harming almost every organ. This pathway is the major cause of death in Covid-19 patients [4]. Cytokine storm with MIS is also called macrophage activated syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (HLH).

Most patients easily overcome the disease even without any medical therapy. For some patients in the early phase inhibition of viral replication with remdesivir may be sufficient. For the majority of patients admitted to the hospital and not discharged within 10 days, not the virus itself but the overshooting immune modulation/exaggeration becomes the challenge.

Therefore, it is not surprising that anti-inflammatory medications, which in part are used intensively in rheumatology, have been also tested in Covid-19 patients. Two of them should be discussed here.

First, steroids; in the RECOVERY study dexamethasone revealed a significant benefit in comparison to placebo [5]. Dexamethasone became a game changer in the treatment of severe SARS-CoV-2 infection for patient already needing oxygen and even more if patients have to be mechanically ventilated. The challenge is to find the right time and appropriate level of immune dysfunction to start with steroid in a viral disease - since steroids definitely have some severe side effects - among others enhancing viral replication or bacterial superinfection would counteract all efforts to beat the disease. The study results from the RECOVERY Trial do not explain at what extent oxygen was used and they did not demonstrate data on virus clearance [6]. Yet we do not have clear guidelines for timing of steroids in severe diseased Covid-19 patients. However, in REVOVERY most patients were included after day seven of disease onset - this is the time at when most patients get admitted to the hospital. That means we may have three parameters to decide prescription of steroids for hospitalized patients.

First, timing: Not too early, seven to ten days after symptom onset may be appropriate, since the maximum of virus replication is probably exceeded [7]. Second, for severe diseased patients (oxygen demand) if the situation cannot be stabilized immediately or prior oxygen naïve patients worsen and oxygen supply has to be started. Third, when already on oxygen - if laboratory parameters typical for MAS or cytokine storm will be present.

What about the second drug? Colchicine a methuselah - more the 2000 years used in human history [8] now experience a revival in modern medicine - not only in rheumatology, endocrinology and cardiology. Colchicine by its "global" interaction with leucocytes is an all-rounder in the battle against inflammation [9]. Not surprisingly several studies focus on Covid-19 and some positive results are already published [10]. Recently the Montreal Heart Institute announced in a press release preliminary results of the COCORONA study [https://www.clinicaltrialsarena.com/news/montreal-heart-institute-tria]. In an analysis of 4,159 patients who had confirmed COVID-19 diagnosis from a nasopharyngeal PCR test compared with placebo, colchicine reduced hospitalizations by 25%, the need for mechanical ventilation by 50% and mortality by 44%. According to the release, all these results were statistically significant. If these results will confirmed by peer reviews, then indeed two old drugs are the shooting stars in the direct treatment of SARS-CoV-2 Infection.

Conclusion

So much could we learn due to immense scientific efforts combined with the possibility of modern information technology. Ironically two old drugs like steroids and probably also colchicine may have best results beating the dramatically consequences of disproportionate cytokine activation.

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Volume 10 Issue 3 March 2021