Research Article

Post Covid-19 Conditions after Dehospitalization according to Therapy

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Abstract

Introduction: SARS-CoV-2 is the name of the zoonosis caused a new disease, called COVID-19. The long persistence of complaints after the initial infection is called "Post-Acute Consequences of SARS-CoV-2 Infection" (PASC).

Purpose: The current prospective study was undertaken to determine whether in-hospital and post-discharge intake of three different molecules: Hydroxychloroquine (HCQ), Rosuvastatin and Melatonin leads to a reduction in complaints, the incidence of new complaints and new hospitalizations during follow-up of patients with severe COVID-19 requiring hospital treatment.

Results: We enrolled prospectively 260 patients hospitalized for COVID-19 and us followed-up 73 of them for one month after discharge. The primary endpoint was the occurrence of PASC and whether this was relevant to the therapy being administered. The effect of three different molecules: HCQ (600 mg / day), Rosuvastatin (20 mg / day) and Melatonin (3 mg / day) was compared. For 65 of the followed-up patients we had data about the persistence of symptoms. Of the 26 patients treated with HCQ one month after discharge from hospital, 4 (15.4%) had persistent complaints, compared to the group of 39 patients not receiving HCQ, in which 18 (46.2%) reported complaints (p = 0.010). Patients taking HCQ had also numerically lower rate of the appearance of new complaints and new hospitalizations, but there was no statistically significant difference between the groups.

Conclusion: HCQ therapy during hospitalization, despite its benefits to the in-hospital course, demonstrated positive effects on Post COVID-19 conditions only when continued for at least one month after discharge at 200 mg tid/ dose. The observed parameters did not show a statistically significant difference in the two groups with / or without Rosustatin and with / or without Melatonin.

Introduction

SARS-CoV-2 is the name of the zoonosis that was transmitted from animals to humans and caused a new disease that changed the world and was called COVID-19. The first cases of the new coronavirus infection were reported in late November 2019 in Central China, Wuhan, after no clear provocative moment, people develop pneumonia, which does not respond to known treatments and is associated with high mortality [1].

Coronaviruses are most common in animals, but there are known cases in which they mutate and begin to infect humans. To date six human-to-human coronavirus infections have been reported. Among them with severe course of the disease were Acute Respiratory Syndrome (SARS) and Middle Eastern respiratory syndrome (MERS) [2,3].

In a short time, COVID-19 spread around the world and was the reason in March 2020, the World Health Organization (WHO) in the person of its general director Tedros Adanom Gebrejesus to declare the spread of COVID-19 a pandemic [4]. A pandemic is an epidemic that covers large geographical regions and continents and is due to a new viral infectious carrier against which the human population has no immunity.

At present, the location of the virus is worldwide. The estimated cases are about 10% of the world's population, data are constantly updated, and the number of infected, hospitalized, and fatal cases is large, regardless of the ubiquitous epidemiological measures [5].

Despite the vaccines being developed, the new mutations in the virus are the reason why the disease cannot be controlled as it subsides and returns in full force, causing great damage to health, economic and social aspects.

Just over a year after humanity's first encounter with COVID-19, the clinical picture and pathogenesis of the disease have been unraveled, but the medical community faced a new, no less important problem, namely, persistent symptoms long after the acute infection.

By definition, Post COVID-19 conditions include all signs and symptoms of COVID-19 that persist after the acute phase (3 to 4 weeks), with no upper limit of duration. Another term for these conditions was introduced by Antoni Fauci and was called "post-acute effects of SARS-CoV-2 infection" (PASC) [6].

According to the WHO, the post COVID-19 conditions can persist indefinitely for months, even years, and have no clear link to the severity of the acute phase. It is known that even patients with a mild course of the disease report persistent symptoms such as fatigue, memory impairment, "brain fog", palpitations, shortness of breath, heaviness in the chest. Many patients with persistent symptoms seek emergency medical care again and are hospitalized.

The symptoms of PASC are multi-organ, with the most common complaints from the nervous system, but also affect the cardiovascular, pulmonary, and urinary systems, gastrointestinal tract, musculoskeletal system, skin [7,8].

Hypotheses for pathogenesis of PASC

There are several hypotheses about the pathogenesis of PASC. The first is direct cell damage by binding SARC-Cov-2 to ACE2, initiating a pathological immune response that leads to increased cytokine production and activation of procoagulant states. It was later found that the cause of prolonged viral replication is the fact that SARS-CoV-2 can be transmitted in a different way from the airways, namely through the gastrointestinal tract, which can be considered a second hypothesis. The gastrointestinal tract is a major immunological organ in the human body and disruption of its microbiome leads to severe dysbacteriosis. Intestinal inflammation exacerbates ACE2 expression, and the virus stays in the gut for much longer, which in turn can modulate immune responses and cause prolonged symptoms. This is proven by an intestinal biopsy, which detects the presence of the virus for months. [8-11].

Covid-19 has also been shown to provoke autoimmune reactions, leading to a more severe course of the disease and persistence of symptoms. The suboptimal immune response results in a higher viral load associated with decreased balance in interferon production (IFN). It has been found that in severe disease the body lacks IFN-beta and the level of IFN-alpha and lambda is reduced [12].

Lymphopenia and unregulated inflammation have been observed in patients with severe COVID-19 and prolonged persistence of the infection because of immune disorders [12]. Thanks to the work of medical experts from around the world, information about the disease is constantly updated and supplemented. Various studies of drugs from many working groups of multidisciplinary teams continue, which follow in detail the clinical picture of patients with COVID-19 find a way to prevent and treat the disease. The diagnostic algorithm is constantly optimized, various protocols for treatment in the acute phase are offered, which so far have contradictory data.

Treatment protocols in acute patients have been divided into two main groups of drugs, some of which are also used for long-term symptoms of COVID-19 [13]:

a. **Antiviral drugs that prevent the replication of the virus** (Remdezivir, Lopinavir / Ritonavir combination, Favipiravir, Umifenovir, Ribavirin, Niclosamide, etc.)

b. **Immune modulators that help the immune system fight the virus or prevent it from causing serious consequences** (Dexamethasone, Hydrocortisone, Convalescent Plasma, Budesonide (inhalation).

c. **Some potential therapies work differently or through multiple mechanisms.**

d. **Drugs with multiple mechanisms:** Chloroquine/ Hydroxychloroquine, Colchicine, Dimethyl fumarate, Angiotensin-converting enzyme / Angiotensin II receptor blocker inhibitors, Statins, Aspirin, Clopidogrel, Anticoagulants, Omebinozine, Vipotizol, Vitiprazole, Ompiprazole, Vipitrazol , Melatonin and others.

e. **Purpose of the study:** The present study was undertaken to determine whether in-hospital and post-discharge administration of Hydroxychloroquine (HCQ), Rosuvastatin and Melatonin resulted in a reduction in complaints, the incidence of new complaints and new hospitalizations during follow-up of patients with severe form of COVID-19, which required hospital treatment.

Materials and methods of the study

The Bulgarian Cardiac Institute was founded in 2007, and investments in health care are focused on reducing cardiovascular mortality and disability by creating a national structure of highly specialized cardiology hospitals and centers in areas with insufficient access to health care.

Our hospital - "Heart and Brain Center of Clinical Excellence ", Pleven, is part of the Bulgarian Cardiac Institute. It is a multidisciplinary university hospital mainly focused on the complex treatment of cardiovascular, cerebrovascular diseases and peripheral vascular diseases. The hospital specializes in innovative health technologies in cardiac surgery, neurosurgery, vascular surgery, and more recently in oncology and genetics. We treat patients from regions of Central North and Northwestern Bulgaria with a population of over 1.5 million people. With the beginning of the pandemic, a ward for the treatment of patients with identified virus COVID-19 was opened in the hospital, which has both the possibility of inpatient treatment and a ward for patients in need of intensive and resuscitation care.

A database including all medical documentation was prepared for each patient after signing informed consent, conducted laboratory and instrumental tests as well as the applied therapy, results from the questionnaires and the information from the interviews of patients by phone.

After the deadline, the collected information was processed and systematized. Due to the great interest of the patients, the monitoring program was extended and continues to this day in the Hospitals of the Bulgarian Cardiac Institute. The program was called "Life after COVID-19".

The methods we used were a survey, a telephone interview, observation.

For hospitalized patients we applied a diagnostic and therapeutic plan according to the protocol of the hospital, corresponding to the good clinical practice.

The choice of medication was determined by the severity of the patient's symptoms and concomitant diseases, as well as his risk profile, and not all medications could be added to the therapy of each patient.

We used the following protocol to treat COVID-19 in hospitalized patients:

a. **Antibiotics:** Clarithromycin, Levofloxacin, Ceftazidime, Meropenem, Doxycycline.

b. **Antiviral drug:** Hydroxychloroquine 3 x 200 mg per day.

c. **Anticoagulant and Antiplatelet drugs:** Nadroparin and Aspirin.

d. **Vitamins and Trace elements:** Vit C; Vit D; Vit B Complex; Magnesium; Zinc.

e. **Famotidine 2x 20 mg.**

f. **Melatonin.**

g. **Statin-Rosuvastatin 20 mg**.

h. **Corticosteroids** - Methylprednisolone 2x 40 mg or more.

i. **Probiotics.**

j. **Infusions with 0.9% Sodium chloride or 5% glucose solution.**

k. **Diuretics - if necessary.**

l. Oxygen **therapy.**

m. **Others: Antipyretics, Antitussive drugs, Analgesics, Therapy for concomitant diseases.**

After dehospitalization in patients who had no contraindications, we continued for 30 days the therapy with HCQ 3 x 200 mg, as well as the intake of Rosuvastatin and Melatonin. As for the Rosuvastatin group, the duration of treatment was determined by the underlying diseases such as coronary heart disease, cerebrovascular disease, etc., in which cases the drug was taken indefinitely according to the recommendations for the treatment of patients with cardiovascular disease. Our goal was to make full use of this protocol, but this was not applicable to all patients in view of the individuality of each patient - comorbidity, risk factors, general condition. The individual

approach was determined by the attending physician and the behavior was discussed at a medical board by a multidisciplinary team.

The patients we followed were divided into six groups according to the therapy at discharge:

group I: patients taking Hydroxychloroquine to the therapy at discharge

group II: patients not taking Hydroxychloroquine

group III: patients taking Rosuvastatin to the therapy at discharge

group IV: patients not taking Rosuvastatin

group V: patients taking Melatonin to the therapy at discharge

group VI: patients not taking Melatonin

For each patient admitted to the clinic we performed: Real-time PCR-based diagnostic test to identify the genetic material of SARS-CoV2 virus, X-ray and / or lung scanner (CT), 12-channel ECG, Echocardiography if deemed necessary, complete blood count, biochemistry, serum electrolytes, D-dimer, natriuretic peptide, if necessary, markers for myocardial damage, markers for inflammation, ferritin, procalcitonin.

Dehospitalized patients were followed up for persistent complaints by phone call and online questionnaire completion. Our priority questions were about the duration of COVID-19 symptoms, whether new symptoms had occurred, and whether patients were rehospitalized.

People also share their overall condition, prolong recovery and time to return to their normal lifestyle. If necessary, a doctor's examination and assessment for rehospitalization were provided. In emergencies, patients were immediately hospitalized again.

Statistical analysis

Statistical analyzes were performed using statistical software SPSS for Windows version 19.0. Continuous variables were presented as mean±standard deviation (SD). The category variables were presented as a percentage. The relationship between treatment and persistence of complaints, new complaints and new hospitalizations was analyzed with a Chi-square test or Fisher's exact test. A two-tailed p value < 0.05 was considered statistically significant.

Results

We enrolled prospectively 260 patients hospitalized for COVID-19 and us followed-up 73 of them for one month after discharge. The main endpoint is the occurrence of PASC and whether it is relevant to the therapy administered during the hospital stay and discharge therapy. The mean age in the group was 67.5 ± 8.3 years, of which 60.3% were male [14]. Most patients have at least one concomitant disease, with nearly three-quarters having hypertension and nearly one-third having ischemic heart disease (Table 1).

Table 1: Risk factors, frequency of major diseases and their relationship to COVID-19.

Indicator	N	%
Ischemic heart disease	24	32,9
Cerebrovascular disease	10	13,7
Arterial Hypertension	53	72,6
Diabetes melitus	19	26
COPD	2	2,7
Dyslipidemia	24	32,9
Peripheral arterial disease	6	8,2
Chronic renal failure	8	11

The effect of three different molecules: HCQ (600 mg / day), Rosuvastatin (20 mg / day) and Melatonin (3 mg / day) was compared.

For 65 of the followed-up patients we had data about the persistence of symptoms. Of the 26 patients treated with HCQ one month after discharge from hospital, 4 (15.4%) had persistent complaints, compared to the group of 39 patients not receiving HCQ, in which 18 (46.2%) reported complaints (p = 0.010). Patients taking HCQ had also numerically lower rate of the appearance of new complaints and new hospitalizations, but there was no statistically significant difference between the groups. (Figure 1)

HCQ therapy during hospitalization, despite its benefits to the in-hospital course, had no effect on Post COVID-19 conditions unless continued for one month after discharge at 200 mg tid dose (Figure 2).

The observed indicators such as persistence of complaints, emergence of new complaints and need for new hospitalizations did not give a statistically significant difference in the two groups with /or without Rosuvastatin and with/or without Melatonin.
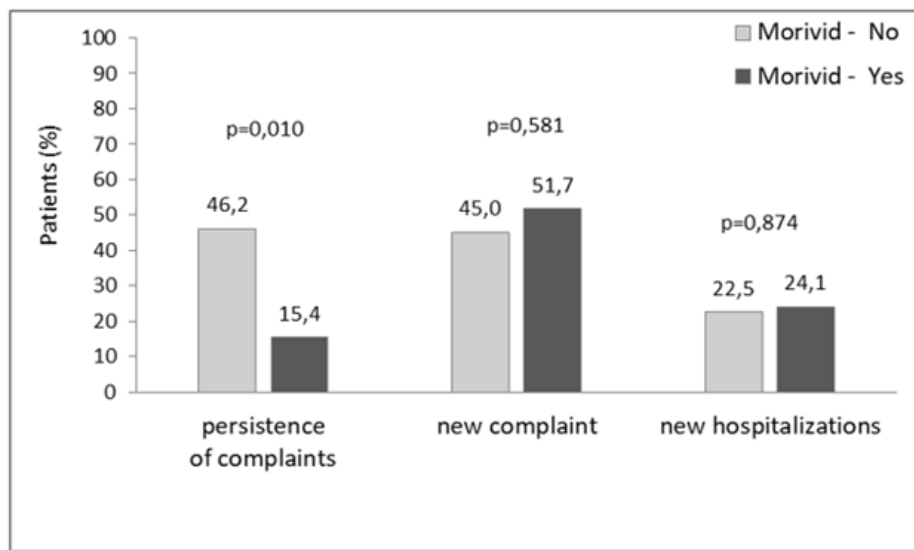
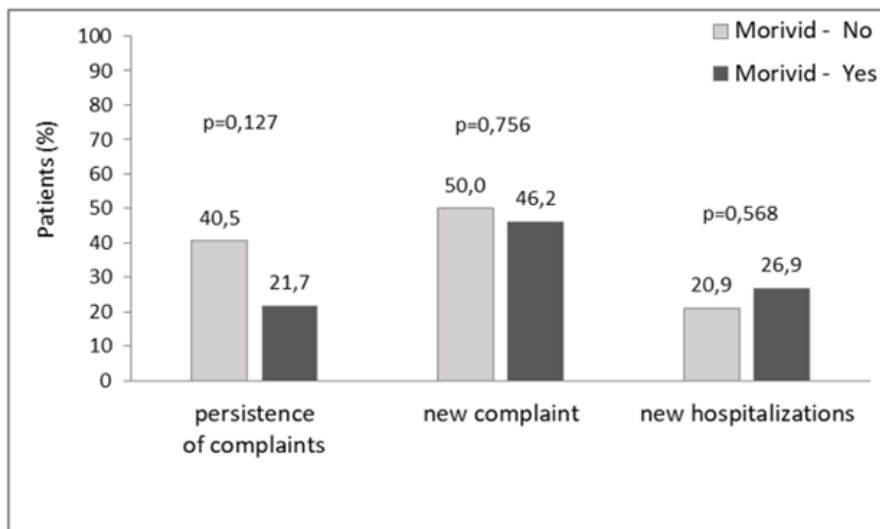**Figure 1:** *HCQ - Discharge therapy.*

Figure 2: *HCQ - Therapy in hospital.*

Safety

Patients receiving **Hydroxychloroquine** were monitored by 12-channel ECG. We did not register QTc prolongation or life-threatening arrhythmias. At follow-up, not all patients were willing to follow the prescribed therapy after discharge from the hospital.

The conclusions we reached were that treatment with in-hospital and post-discharge treatment with Rosuvastatin did not show a statistically significant difference group III receiving Rosuvastatin versus group IV-not receiving Rosuvastatin) in terms of persistence of complaints, new complaints, and new hospitalizations month after discharge (Figure 3&4).

Melatonin has a beneficial effect in the treatment of patients with COVID-19, but there is no statistically significant difference from the group of patients who did not take melatonin compared for the endpoints of our study: persistence of complaints, new complaints, and the need for new hospitalizations (Figure 5&6).
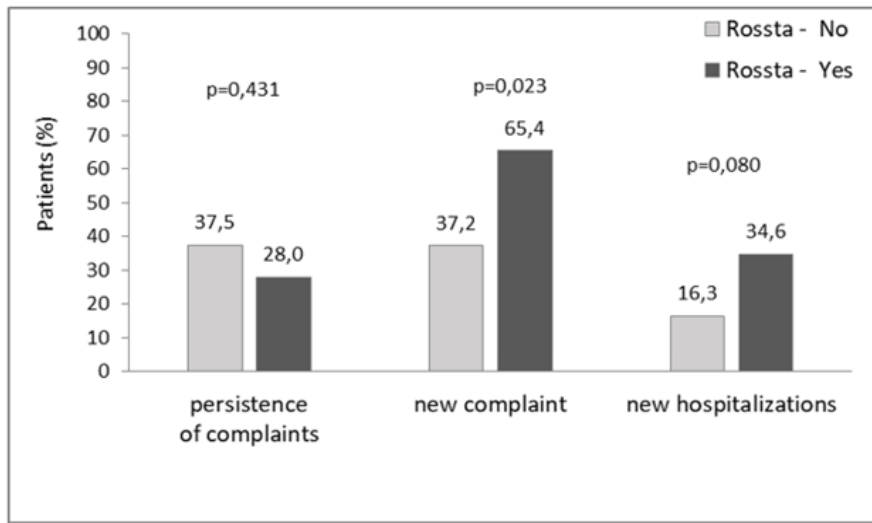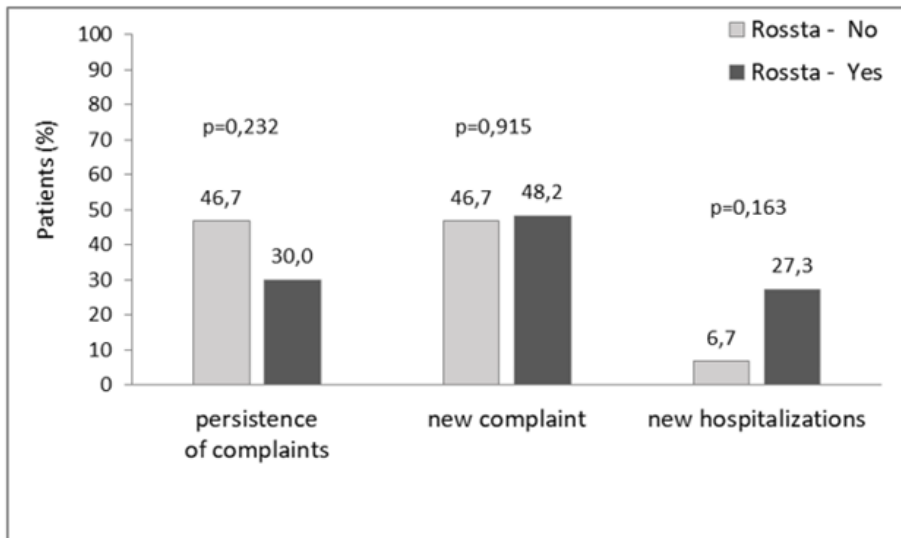
Figure 3: *Rosuvastatin - Discharge therapy.*

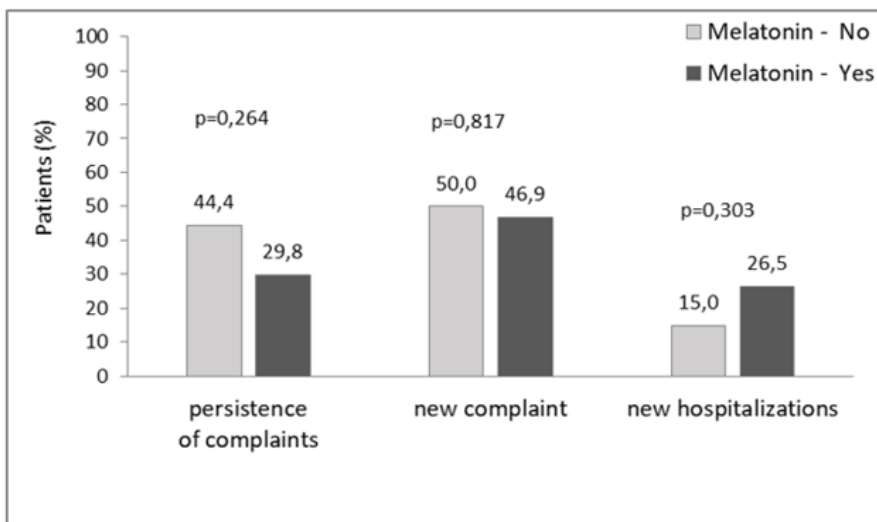**Figure 4:** *Rosuvastatin- Therapy in hospital.*

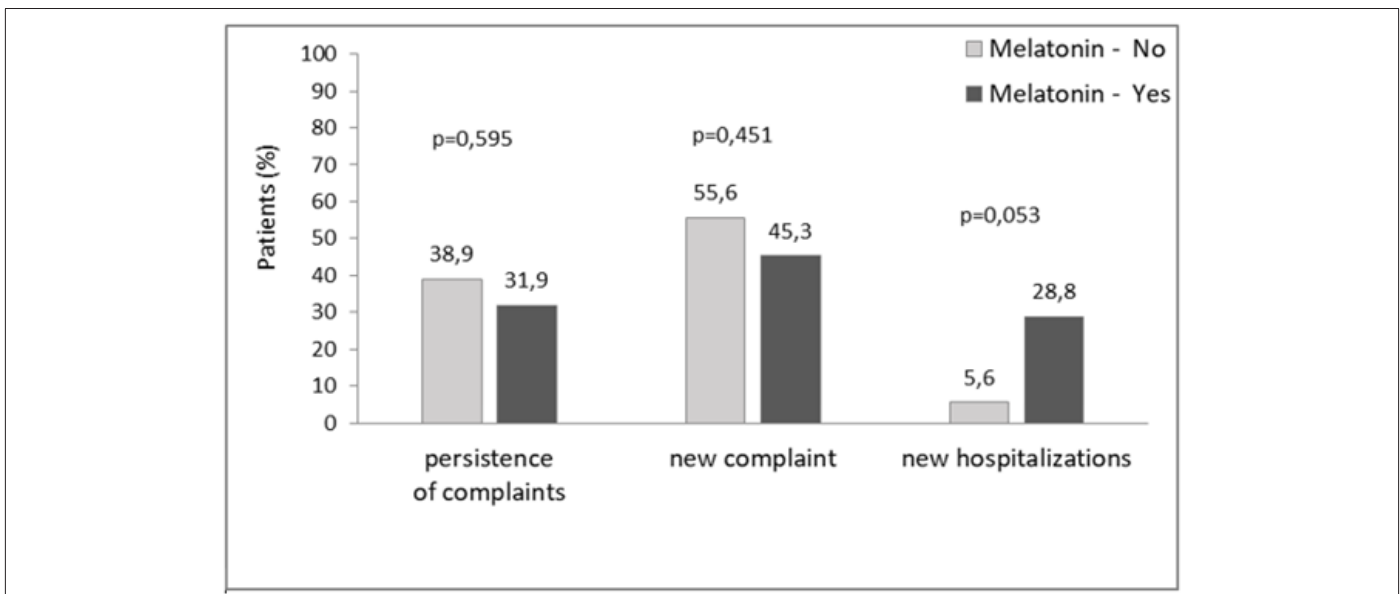**Figure 5:** *Melatonin- Discharge therapy.*

Figure 6: *Melatonin –Therapy in clinical.*

Discussion

Within a year of the Pandemic, the effects of post-COVID-19 syndrome have been shown to be as great as those of the acute phase of the disease.

From the data presented above from the study of three molecules: Hydroxychloroquine, Rosuvastatin and Melatonin on their effect on PASC, our research center came to the following conclusions:

HCQ

The benefits of hydroxychloroquine in patients with identified COVID-19 indicate a milder course and a shorter and/or no post COVID-19 syndrome. Clarifying patients according to their risk profile and excluding underlying arrhythmias before starting the drug can minimize the risk of complications. We recommend frequent and precise monitoring of indicators, conducting imaging studies and treatment protocols, which rely on prevention and compensation of concomitant diseases. Frequent ECG monitoring in the patients makes the molecule recommended, and its benefits outweigh the risks. The data are based on a study conducted by the Bulgarian Cardiac Institute.

Although scientific data were manipulated and the effects of HCQ were reported to be ineffective, this information was subsequently withdrawn, but the negative attitude remained in much of the medical community [15]. According to the literature, no major adverse reactions have been reported with any of the HCQ studies performed worldwide. Many in vivo and in vitro studies with Hydroxychloroquine are ongoing and positive evidence for prophylaxis and milder course is encouraging. Evidence of this is the huge number of patients in trials in the United States, China, France, Algeria, etc., the number of patients who passed through our center, as well as patients treated with HCQ due to autoimmune conditions such as systemic lupus and rheumatoid arthritis in the years before COVID-19 the pandemic [16].

One month after discharge most patients taking HCQ had a beneficial response to symptoms, less recurrence of new symptoms, and a lower frequency of rehospitalizations. Only one patient had a fatal outcome. Unlike discharge therapy, HCQ therapy during hospitalization, despite its benefits in-hospital course, had no effect on Post COVID-19 conditions unless continued for one month after discharge at the same 600 mg dose. days.Particularly good results on the effects of long-term COVID-19 were observed in patients who continued to receive Hydroxychloroquine for one month after discharge from the hospital.

The beneficial effect of Hydroxychloroquine that we observed is not accidental and is due to the pathogenetic mechanism of action of the drug at several levels:

1. HCQ interacts with the SARS-CoV-2 receptor (ACE2 receptor) and thus prevents the virus from attaching to the receptor.

2. HCQ reduces the acidity of the medium, thus stopping the entry of the virus through the membrane of the host cells.

3. If the virus enters the cells, HCQ interferes with the release of the viral genome.

4. HCQ interacts favorably with the immune system.

5. HCQ inhibits the development of the cytokine storm in severe cases of COVID-19.

6. The mechanisms of action of HCQ are common and have not been affected to date by various mutations in the virus [16-18].

Rosuvastatin

Over the years, statins have proven their effect and role in reducing the risk of cardiovascular events. According to the rules of good clinical practice, patients at high and very high cardiovascular risk should receive statin therapy. Recommendations for targeted LDL cholesterol levels to achieve the desired target effect are increasingly lower [19]. These properties are due to the known anti-inflammatory and immunomodulatory actions, it is with this effect that they are included as a treatment of patients with COVID-19 in many protocols [20].

Rosuvastatin was not found to be relevant to the manifestations of PASC. Our explanation is that the group of patients taking a statin is larger and therefore the frequency of new complaints and new hospitalizations is higher, on the other hand, patients who must take the molecule have a proven high cardiovascular risk, with underlying cardiovascular diseases in which the initial infection with the virus leads to decompensation of the underlying disease and the appearance of persisten COVID-19 syndrome. We recommend that Rosuvastatin therapy be maintained in patients with concomitant medical conditions. The use of rosuvastatin in patients without dyslipidemia and a high-risk profile would not be harmful, but there are no proven significant benefits in patients with post-COVID-19 syndrome on recent studies with this class of drugs.

Melatonin

The low level of melatonin in the blood of adults is condition associated with a more severe course of the disease, compared to children in whom the infection is almost asymptomatic, due to high levels of melatonin. Bats, the main carriers of coronavirus, also have elevated levels of melatonin, which determines the higher resistance to viral replication of coronavirus infections. Studies have shown that melatonin reduces lung fibrosis. This is due to the anti-inflammatory and antioxidant properties of the molecule, i.e., it reduces the levels of oxidative stress [21].

The results we analyzed give us reason to believe that the intake of Hydroxychloroquine, but not that of Rosuvastatin and Melatonin has a positive effect on the monitored indicators: persistence of symptoms, the appearance of new symptoms and the need for new hospitalizations in connection with post Covid-19 conditions.

Additional studies are needed both with the molecules and with a larger cohort of patients in order to optimize the treatment protocol in patients with COVID-19 which would reduce the effects of long-term persistence of shortness of breath, fatigue, palpitations, etc., symptoms. Understanding the pathogenesis of PASC may provide answers to additional questions to guide the medical community to the right approach to behavior and reduce the effects on sufferers.

COVID-19 is a multi-organ disease in which the cardiovascular system is involved. This defines the role of cardiologists in the against the disease. Based on the number of patients who have passed through our center in the consequences of the disease, we believe that the place of the "COVID-19 team", including a multidisciplinary team on infectious diseases, cardiologist, neurologist, imaging doctor, anesthesiologist, psychologist, rehabilitator, and others play a key role in combating PASC. Specialists could reduce the risk of a complicated course of the disease and reduce mortality.

All these measures would reduce the collapse of the health system, which in turn would save more lives and reduce economic costs.

Conclusion

 The results we analyzed give us reason to believe that HCQ has a positive effect on the PASC in cases where HCQ treatment was continued post-discharge. During follow-up after dehospitalization, the majority of patients taking HCQ had a beneficial resolution of symptoms, less ocurrence of new symptoms, and a lower frequency of rehospitalizations, the latter two not reaching statistical significance.

Rosuvastatin and Melatonin did not reduce the symptoms of PASC.

Ethics

The clinical trial protocol has been reviewed and approved by the Local Ethics Committee. All research procedures adhere to the principles of the Declaration of Helsinki. Informed consent for inpatient treatment of COVID-19 and collection and analysis of personal data was obtained from all patients.

I declare that we do not have a Conflict of Interest and the article has not been published in other journals.

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