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TO ASSESS THE PRACTICAL IMPORTANCE OF STUDYING THE EFFECT OF STATINS ON EFFECTIVENESS IN THE TREATMENT OF PATIENTS WITH CHRONIC CORONARY HEART DISEASE WITH COVID-19

Atakhanova S. K.
Master of Cardiology, 3rd Degree

Vakhabov B. M.
Candidate of Medical Sciences, Associate Professor
Department of Faculty Therapy

Bektasheva G. M.
5th Year Student, Faculty of Medicine
Andijan State Medical Institute Andijan. Uzbekistan

Abstract
The pandemic of the new coronavirus infection (COronaVIrusDisease 2019) COVID-19 and the quarantine measures that followed it, in particular, the self–isolation of the population, have left a serious imprint on the lifestyle of people, especially those suffering from chronic non-communicable diseases (CNID). First of all, this could affect the quality of the therapy they constantly take. For certain reasons, during the COVID-19 pandemic, such patients could have a number of problems with contacting the appropriate specialist doctor, receiving or purchasing medications they constantly take (LP). A number of recently published studies have reported the occurrence of such problems in dermatological patients, in patients with autoimmune inflammatory rheumatic diseases. The aim of the present study was to find out how the adherence to constant therapy has changed in patients with chronically stable coronary artery disease (CHD) in self-isolation during the COVID19 pandemic.

Keywords: adherence, pharmacotherapy, COVID-19 pandemic, period of self-isolation, stable coronary artery disease, telephone survey.

Introduction

In the situation of a pandemic caused by coronavirus infection, a special risk group consists of patients with cardiovascular diseases (CVD), which are often found in the population. The spread of coronavirus infection is particularly dangerous in relation to decompensation of existing chronic diseases, specific damage to the cardiovascular system, especially in the case of severe coronavirus infection and a high risk of adverse outcomes in patients with CVD.

The combination of coronavirus infection with CVD creates additional difficulties in diagnosis, determining priority tactics, changing the routing of patients with urgent conditions, and choosing therapy. The situation is complicated by a lack of information, a significant volume of daily, often contradictory, publications on these issues and the extremely high importance of solving these issues for clinical practice.

To date, a large amount of information has been published and continues to be published in leading medical journals, online resources and social networks. These are mainly descriptions of clinical cases and data from observational prospective and retrospective clinical studies and their meta-analyses. At the same time, hundreds of randomized clinical trials have been initiated, which will provide convincing answers to existing questions, especially regarding patient management tactics. The submitted document reflects the position based on the available data and will be updated as new evidence becomes available.

Goal

To determine the dynamics of adherence to continuous therapy in patients with chronic coronary heart disease (CHD) in self-isolation during the COVID-19 pandemic.

Material and Methods

In the period from 05.05.2020 to 14.05.2020, a telephone survey was conducted to assess adherence to therapy with cardiovascular drugs during self-isolation in patients who completed participation in the ALIGN study. ALIGN (TherApy in stabLe Coronary Artery dIsease Patients According to Clinical GuideliNes) study (NCT04162561; www.ClinicalTrials.gov) is a cohort prospective observational study. In this study, in patients with stable coronary heart disease, adherence to treatment after correction of pharmacotherapy (FT) was studied in accordance with current clinical recommendations (CR), the effectiveness of this therapy and its impact on quality of life, depending on adherence indicators. The study consisted of an inclusion visit (V0) and V1, V2 visits performed 3 and 12 months after V0. The ALIGN study protocol and questionnaires have been approved by an Independent Ethics Committee. In addition, the Independent Ethics Committee reviewed and approved the execution of an additional telephone survey after the completion of the study. The study involved primary patients with proven stable coronary heart disease, whose data were included in the outpatient registry of patients with cardiovascular diseases and their risk factors. All patients gave informed consent to the use of personal data, as well as to participate in the study and surveys related to it. Adherence was assessed using an original questionnaire – the adherence scale of the National Society for Evidence-Based Pharmacotherapy (NODF). Patients who fully complied with medical recommendations regarding FT were considered committed. Any violation of the intake regimen or an independent change in the daily dose of LP was regarded as partial adherence. Patients who completely stopped taking one or more drugs were considered to be unaffected. If necessary, dichotomous division into subgroups, patients with partial adherence and non-committed patients were combined into one subgroup of non-committed patients. In addition, the participants of the telephone survey were divided into two

subgroups – with a deterioration in commitment during the period of self-isolation against the background of the COVID-19 pandemic and without changes in commitment. Adherence was determined both to the whole FT as a whole (general adherence) and to the drugs of each group specifically (to the intake of disaggregants, statins, beta-blockers, etc.). It should be noted that changes in adherence were diagnosed during the period of self-isolation, and not those that occurred earlier. Of the patients included in the ALIGN study (n=71), visits V0, V1 and V2 were performed in 39 people, it was among these patients that a telephone survey was conducted during the COVID-19 pandemic. During telephone contact, adherence to the recommended cardiovascular PT (general and to drugs of individual drug groups) and its changes in self-isolation conditions were determined. The study cohort included 37 men (94.8%) and 2 women, the average age of patients was 67.6±8.5 years.

The results of the study

The SARS-CoV 2 coronavirus is a single-stranded RNA virus coated with a lipid membrane. The virus has four structural proteins: a nucleocapsid protein, a membrane protein, a shell protein and a spike protein (S-glycoprotein), which provides attachment to the angiotensin converting enzyme receptor 2 (APF2) and CD 147 [3]. It is necessary to consider the interaction of the virus with the cell membrane in order to understand the possible role of statins in countering the virus.

Lipid rafts (sites) are subdomains of the plasma membrane of cells enriched with cholesterol and glycosphingolipids. The important role of membrane lipids in the attachment of viruses, including some coronaviruses, to host cells has been reported [4, 5], as well as the fact that an increase in the concentration of cholesterol in lipid rafts increases viral infectivity [6]. Lipid rafts play a role in the interaction of S-protein ("spike") and the APF2 receptor, as well as for the processes of viral endocytosis [7]. The role of cholesterol in virus penetration has been studied for several coronaviruses, including SARS-CoV [7]. Cholesterol present in the cell membrane and viral envelope contributes to the replication of the coronavirus, acting as a key component in the penetration of the virus [6].

At the same time, it was noted that cholesterol levels in patients with COVID 19 were extremely variable. In particular, in the acute phase of COVID 19, the levels of total cholesterol and LDL decreased sharply compared to the baseline level [28]. On the other hand, in SARS-CoV, a sharp decrease in cholesterol levels led to a significant decrease in the concentration of viral microRNA [9] and impaired fusion of the virus with the cell membrane [7].

Statins inhibit cholesterol biosynthesis by inhibiting HMG-CoA reductase and modulate the composition of cell membrane lipids.

Atorvastatin reversed many of the lipid raft-related changes caused by systemic lupus erythematosus [3]. In this regard, there is reason to assume that the use of statins to prevent changes in the lipid membrane in host cells caused by COVID 19 infection may reduce the degree of viral replication.

Although APF2 is especially prevalent in the heart and kidneys [3], where it plays an important role in blood pressure control [2], it is also present in other tissues, including the lungs [3]. For

this reason, dysregulation of APF2 levels can lead to undesirable and even fatal results. For example, impaired expression of APF2 increased vascular permeability and pulmonary edema, contributing to the further progression of lung damage [3]. Therefore, therapeutic strategies based on the interaction of the virus with APF2 and other receptors are proposed [34]. In particular, statins are known to increase the level of APF2 in tissues — in the model of experimental atherosclerosis, atorvastatin increased the levels of APF2 protein in the heart and renal tissue [5]. The CD 147 cellular receptor can also bind to S-glycoprotein, the "spike" of the SARS—CoV 2 coronavirus [36]. Accordingly, another pleiotropic effect of statins is the modulation of CD 147 expression, structure and function. Atorvastatin reduced CD 147 levels and increased the stability of atherosclerotic plaques in the model of experimental atherosclerosis [37]. Thus, there is evidence that statins, by modulating CD 147 and APF2 receptors in human cells, can disrupt the ability of the virus to infect.

One of the most characteristic pleiotropic effects of statins is their anti-inflammatory effect [3]. It is believed that the restriction of vascular inflammation, in addition to their lipid-lowering effect, contributes to the beneficial effect of statins on cardiovascular outcomes [38]. Atorvastatin inhibits the activation of NF-kB-mediated cytokine induction induced by angiotensin II or tumor necrosis factor-α [39]. Several studies have shown the ability of HMG-CoA reductase inhibitors to regulate inflammasome NLRP3 inflammation [40]. Statin treatment also suppressed the expression of cytokines NLRP3 and interleukin 18 (IL 18) and IL 1ß in patients with CVD [41]. Therefore, the anti-inflammatory effect of statins, in particular against NF-kB and the inflammasome NLRP3 pathways, will be an important component of the pleiotropic effect of these drugs in COVID 19.

The coagulation system can limit the spread of pathogenic microorganisms during severe infections, an example of which is a large number of viruses such as HIV, Dengue virus or Ebola [42]. Nevertheless, in acute viremia, a violation of coagulation is often found.

A recent cohort study with 96032 hospitalized COVID 19 patients showed a beneficial effect of statins on mortality. There were more survivors in the group with HMG-CoA reductase inhibitors than without them (10.0% vs. 6.9%, $p < 0.0001$). Statin use was an independent predictor of low hospital-acquired mortality (relative risk, 95 % CI: 0,793, 0,736–0,855) [46]. The most recent evidence of the effectiveness of these drugs was a large retrospective cohort study in 13,981 patients with COVID 19 to determine the relationship between statin use and clinical outcomes in the hospital (1,219 took statins and 12,762 did not take drugs of this class) [47]. Since the study was uncontrolled, the groups differed in age and the presence of concomitant diseases. Of the statins, atorvastatin (83.2% of all statins) and rosuvastatin (15.6%) were most often used. As a result, mortality by the 28th day of follow-up from the moment of hospitalization was lower in the statin group (5.5% vs. 6.8%, respectively, $p = 0.046$).

Discussion

Statins can be used in clinical practice as a pathogenetic or additional treatment method for dyslipidemia and coronary heart disease, as well as for diabetes mellitus, cerebral circulatory

disorders, hypertension, chronic kidney disease, various types of cancer, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease and even some infectious diseases (malaria, fever Ebola, influenza virus-related diseases, or MERS) [48] as part of the main indications for this class of drugs.

Therefore, based on the large number of pleiotropic effects and the widespread use of HMG-CoA reductase inhibitors worldwide, an assumption has emerged about the possible positive effect of therapy with these drugs in patients with COVID 19. In this review, we examined some pleiotropic effects of statins, such as modulation of APF2 and CD 147 receptors, lipid cell rafts, restriction of inflammatory response and hypercoagulation (Fig. 2). In addition to the issues discussed, a decrease in sympathetic tone can be noted against the background of the use of drugs of this class [49], and the fact that some HMG-CoA reductase inhibitors can serve as potential inhibitors of the main protease SARS-CoV 2 [50]. In two cohort studies, a decrease in mortality was shown when taking statins in patients with COVID 19 [46, 47]. However, at the moment, the use of statins in COVID 19 still falls under the “off-label" category. Currently, several randomized clinical trials are being conducted with COVID 19 patients using simvastatin in combination with the JAK 1/2 inhibitor ruxolitinib (NCT04348695) and atorvastatin (NCT04380402) to confirm this theory. Nevertheless, it is necessary to keep in mind the possible appearance of muscle symptoms in COVID 19, which may mimic the side effect of this group of drugs.

Conclusion

In conclusion, prove from different information and thinks about proposes that there appears to be an interlink between COVID-19 and CHD, which have been examined comprehensively in this paper. A conceivable speculation may be the truth that ischemic assaults are more inclined in patients that are influenced with atherosclerosis, as the infection forcefully triggers the incendiary pathways and leads to hypercoagulation within the blood, clarifying Moreover, conceivable thinking behind the relationship between COVID-19 and cardiovascular wellbeing may be due to the tall expression of ACE-2 receptors within the myocardium, which may in portion contribute to the myocardial wounds watched in patients influenced by SARS-CoV-2. Creator composed the paper, basically evaluated the paper, made last proposals; M.B.: Proposed the thought, proposed the structure of the paper, to begin with free analyst. All creators share duty for the choice to yield the original copy for distribution. All creators have perused and concurred to the distributed adaptation of the composition. Subsidizing: This inquire about gotten no outside financing. Educated Assent Articulation: Not appropriate Clashes of Intrigued: The creators announce no strife of intrigued.

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