

If NUCs protect SARS-CoV-2 infection?

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Abstract

We present data from our 4-month research for the effect of Tenofovir, Lamivudine and Entecavir on protection from SARS- CoV-2. We analyzed with rapid antibodies test the status of all patient with liver disease. The total number of examined patients is 478. Their average age is $55,19 \pm 12,68$. Just 17 from 343 (5%) of those on therapy have antibodies for SARS- CoV-2. 8 from the Tenofovir- treated patients were IgM (+) on a rapid test and 3- IgG (+)(5%). From those on therapy with Lamivudine, 5 were IgM (+) and 1- IgG (+) (6,5%). No patients on Entecavir were positive for IgM or IgG antibodies for SARS-CoV-2. In contrast 14 from 135(10,3%) from the patients without therapy have antibodies. We divided the patients by decades. In almost all decades the percentage of antibodies is two times lower in those on therapy than in those without.

Keywords: COVID-19, Chronic liver disease, HBV, treatment

Introduction

Coronaviruses are part of the subfamily Orthocoronavirinae, in the family Coronaviridae, order Nidovirales, and realm Riboviria. They are RNA-viruses. Transmission is usually via airborne droplets to the nasal mucosa. 80.9% of the patients infected with SARS- CoV-2, have mild symptoms such as acute, mild upper respiratory infection (common cold) and recover without therapy (2). The older and those with comorbidities can develop serious complications and that is the reason behind the attempts to find a cure for the

disease.(1) By now the antiviral treatment for SARS-CoV-2 is not defined. Attempts are being made to find a cure from the available medications such as Remdesivir, Lopinavir/ritonavir, Interferons, Corticosteroids, Hydroxychloroquine, IL-6 inhibitor (3). Some of the discussed efforts are with Tenofovir, Lamivudine or Entecavir, which have been used for the treatment of Chronic Hepatitis B.

Aim

To analyse the frequency of anti- SARS- CoV-2 antibodies in Bulgarian patients with chronic liver disease.

Materials & Methods

We analysed with rapid test the SARS-CoV-2 status of all patients with liver disease, who were monitored at the Clinic of Gastroenterology for the period from April 2020 to August 2020. The total number of examined patients is 478. Their average age is $55,19 \pm 12,68$. 314(66%) of them are men and 164(34%) - women. According to the antiviral treatment the patients were divided into two groups: the cohort of HBV-patients, treated with Tenofovir, Lamivudine or Entecavir (Group A, n=343), and a group of patients with various other chronic liver diseases without antiviral therapy (Group B, n=135). None of the monitored patients had a history for SARS-CoV-2.

Results

In this study we included 343 HBV- patients, treated with nucleotide/nucleoside analogues (NUCs)- 221 were receiving Tenofovir(T), 93 on Lamivudine(L) and 29 on Entecavir(E). In this group 13 (3,8%) patients were positive for SARS- CoV- 2 IgM antibody (8 T and 5 L) and 4 (1,2%) were positive for IgG antibodies on rapid test (3 T and 1 L). No patients on Entecavir were positive for IgM or IgG antibodies for SARS-CoV-2. In total, 17 from 343 patients (5%) on antiviral were positive on rapid test for COVID- 19.

Group B consists of 135 patients. From them 9 were IgM (+) pos., 3 IgM (+) pos. and IgG (+) pos., and only 2 IgG (+) pos. for COVID-19. That makes 14 patients positive for any SARS-CoV-2 antibodies, or 10,3%. In all 478 patients 25(5,2%) were IgM (+) pos. for COVID-19 and 9 (1,9%) were IgG (+) pos – Table 1.

	Group A n = 343	Group B n=135	Group A+B n=478
Pos (+) IgM	n = 13 (3,8%) 8 Tenofovir 5 Lamivudine	n=12 (8,9%)	n=25(5,2%)
Pos (+) IgG	n = 4 (1,2%) 3 Tenofovir 1 Lamivudine	n= 5 (3,7%)	n=9(1,9%)
Neg. IgM+ IgG	n=326(95%)	n=118(87,4)	n=444(93%)

Table 1: Distribution by SARS-CoV-2 antibody status

We divided the patients by decades and presented them in the table below. We found that the percentage of antibodies in patients from Group A in all age groups is two times lower than in those in Group B. Therefore, we can say that, regardless of age, in patients on therapy, there is a factor that prevents the virus

from entering the body of patients. The difference is in decades 20-29 years and 70-79. In the decade 20-29 the % of patients positive for antibodies in Group B is 0%. It may be due to the small number of Group B patients in this range - 4 patients. In the decade 70-79 the % positive patients from Group A is higher than the Group B. It may be due the fact, that all the positive patients from Group A (3 patients) have cirrhosis, arterial hypertension and one of the four patients have chronic lymphocytic leukemia and is on therapy with Chlorambucil. These comorbidities may affect the susceptibility from SARS-CoV-2.

Age	Total	Total positive	NUC- HBV total	NUC- HBV positive	No NUC total	No NUC positive
20-29	10	1 (1%)	6	1 (16,7%)	4	0 (0%)
30-39	52	2 (3,8%)	37	0 (0%)	15	2 (13,3%)
40-49	100	5 (5%)	75	2 (2,7%)	25	3 (12%)
50-59	146	10 (8,9%)	82	6 (7,3%)	30	4 (13,3%)
60-69	58	7 (4,8 %)	106	3 (2,8%)	40	4 (10%)
>70	32	7 (12%)	37	4 (11%)	21	3 (14,3%)

Table 2: Percent of Patients with Antibodies divided by decades

Discussion

We found a frequency of 5% for patients with Chronic Hepatitis B on therapy, which corresponds to the PCR frequency for the country (4%). Because the SARS-CoV-2 - PCR- frequency in Bulgaria is 4%, it is possible that this 10% IgM or IgG positive patients with various other chronic liver diseases reflect the real rate of the infection in the population. It is expected, that the frequency of positive patients is higher with the rapid antibodies test, because it includes bigger time interval, asymptomatic patients, excluding technical error, when taking the sample. The total frequency is about 7%. It gives the impression, that the patients on NUCs therapy have two times lower frequency from the other group. That is why we could say, that there is indeed a factor, which lowers the risk from infection from SARS-CoV-2.

After a randomized epidemiological study of antibodies in Plovdiv (4), in which 800 people took part, it became clear that the incidence of antibodies is 2%. Until August 2020, the frequency of positive PCR tests in Bulgaria is 4.5%. After reference, the rate of PCR positive tests in Greece is 0,8%, in Serbia, it is 4%, in North Macedonia - 11%, in Romania - 4,4%.

Following a literature review, we found an article called "Incidence and Severity of COVID-19 in HIV - Positive Persons Receiving Antiretroviral Therapy" from Annals of Internal Medicine (3), describing the incidence of HIV-positive patients receiving TDF / FTC. Of 77 590 HIV-positive persons receiving antiretroviral therapy, 236 were diagnosed with SARS-CoV-2, 151 were hospitalized, 15 were admitted to the ICU, and 20 died. The risk for SARS-CoV-2 hospitalization rate was 10.5 (CI, 5.6 to 17.9) among those receiving TDF/FTC. These HIV-positive patients have a lower risk for SARS-CoV-2 and related hospitalization than those receiving other therapies. No patient receiving TDF/FTC was admitted to the ICU or died.

In our study, we observed that Tenofovir patients, who were more numerous, had a lower incidence rate. From this we can conclude that Tenofovir therapy has the greatest effect in the prevention of SARS-CoV-2.

No morbidity was observed with Entecavir, but this was also due to the smaller number of patients enrolled in the study.

Conclusion

We observe that until now, there is a significant difference in morbidity between patients with chronic liver disease with and without NUCs therapy. As therapy for SARS-CoV-2 with virustatics being discussed, we speculate that treatment with Tenofovir, Lamivudine and Entecavir could offer relative prevention. Further investigation is needed.

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