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THE COMPARISON OF THE EFFICACY OF DIFFERENT TREATMENT SCHEMES FOR PATIENTS WITH CHRONIC HEPATITIS C IN COMBINATION WITH HIV INFECTION

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Abstract

The purpose of the study was to establish the clinical, laboratory and immunological features of HIV infection on the background of chronic hepatitis C (HCV) and / or B (HCV), as well as to compare the effectiveness and safety of interferon-containing and interferon-free HCV therapy in HIV-infected people. Patients and methods. 40 patients with HIV monoinfection were examined, 77 patients were with combined HIV / HCV infection and another 18 patients with a combination of HBV, HCV and HIV infection. The therapy of patients with CHC was carried out using a triple interferon-containing regimen (sofosbuvir 400 mg 1 time per day orally + pegylated interferon alfa-2a at a dose of 180 mcg subcutaneously 1 time per week + ribavirin in dosage depending on weight: 1000 or 1200 mg / day in persons <75 kg or ≥75 kg, respectively), or a pangenotypic combination of direct-acting antiviral drugs - sofosbuvir 400 mg and velpatasvir 100 mg once daily orally. The duration of therapy for both schemes was 12 weeks. Results. In HIV monoinfection, dyspeptic syndrome was registered 2,9-3,3 times, and hepatosplenomegaly – 2,0-2,2 times less often than in the combination of HIV infection with CHC or HCV and CHC (p <0,001). Among HIV/HCV- and HIV/HCV /HBV-co-infected, the individuals with an initial level of $CD4^+$ - lymphocytes <350 cells / ml were registered 2,2-2,6 times more often than among HIV-monoinfected (p <0,01). The average strength and strong feedback between the indicators of $CD4^+$ - lymphocytes and the viral load (HV) of HIV (in patients with HIV only – r = -0,720, p <0, 05 with concomitant CHC - r = -0,763, p <0, 01, with a combination of HCV, CHC and HIV - r = -0, 552, p <0, 05). It indicates the establishment of a pathological process and the balance between the immune system and the activity of the viral process. In the absence of concomitant viral hepatitis, the degree of liver fibrosis on the METAVIR F0 scale was determined significantly more often than in HIV / HCV and HIV / HCV / HBV coinfection, and there were no cases of liver cirrhosis at all. The ratio of HCV genotypes in our study was similar for other regions of Ukraine: 1b dominated, genotype 3a was established in every fourth to fifth patient, it was rarely identified, and only in single patients the 2nd HCV genotype was detected. Conclusions. In case of infection with 1b or not typed HCV genotype, the triple therapy after 1 month provided normalization of aminotransferase activity in 83,3% of patients, and after 12 weeks - in all patients. Instead, the results of HCV viral kinetics in the process of antiviral therapy (AVT) lagged behind the dynamics of cytolysis syndrome. A sustained virological response (SVR) was achieved in 75, 0% of such patients, and in 2a of 3a in the case of HCV 3a genotype infection. The dynamics of ALT and AST activity in most cases was parallel to the viral kinetics of HCV. Only in the process of treatment of CHC by interferon-containing three-component scheme side effects and side effects of therapy are noted: hyperthermia, malaise, anorexia, weight loss, depression, decreased white blood cells and lymphocytes and the resulting decrease in the absolute number of $CD4^+$ - lymphocytic lymphocytes cells did not change. Sofosbuvir + velpatasvir therapy proved to be much more effective and safer: CBV was found in 100, 0% of HIV / HCV patients in non-HCV genotype 3 and in 2 of 3 patients infected with HCV genotype 3a. The concentration of aminotransferases, even in the absence of SVR, did not exceed the upper limit of normal (VMN). The patients tolerated this treatment well; only in isolated cases the moderate headache, fatigue and nausea were noted, which could be due to other reasons.

Key words: chronic hepatitis C, chronic hepatitis B, HIV infection, combined infection, features of the course, treatment.

Introduction:

HIV infection and chronic hepatitis C remain relevant today due to high morbidity, common routes of transmission, polymorphism of clinical manifestations, high risk of adverse effects and significant economic losses due to the predominance of infected people of working age [1].

According to the World Health Organization (WHO), hepatitis C virus (HCV) infects between 500 million and 1 billion people worldwide, so HCV is considered the etiological cause of the second socio-economic epidemic of viral origin after HIV infection [2].

UNAIDS estimates that since the beginning of the HIV epidemic, 78 million people in the world have been infected with HIV and 35 million have died from AIDS. At the end of 2017, there were about 37 million people living with HIV on the planet [3].

It is estimated that between 4,3 and 6,6 million people are infected with HIV each year, 8 to 35 million are infected with hepatitis viruses with a parenteral mechanism, and about 13 million people die each year because of HIV, hepatitis B and C. [4].

There are conflicting data in the literature on the interaction of HCV and HIV on the course of the infectious process in co-infected people. The state of immunosuppression in HIV / HCV-infected patients is accompanied by active replication of HCV complicates the course of the disease and leads to the progression of liver damage and cirrhosis. It has been proven that HIV accelerates the progression of CHC in the late stages of liver disease and complicates its treatment. In turn, CHC has a negative effect on the use of antiretroviral drugs for the treatment of HIV infection and on the life expectancy of patients. The progression of HIV infection depends on a number of factors, including the level of $CD4^+$ -T-lymphocytes, the load of HIV, the patient's age at the time of infection, race and others. Among the adverse factors influencing the course of CHC are known high viral load and the presence of immunosuppression caused by immunoglobulin deficiency, uremia, old age, excess iron in the liver, coinfection with other viruses, including HIV [4].

According to the guidelines of the American Association of Studying of Liver Diseases (AASLD) and the American Association of Infectious Diseases (IDSA), it is recommended to treat all patients with chronic HCV infection, except when the life expectancy is unfavorable (e. g, comorbidities). The studies show that treatment in the early stages of the disease gives better results than treatment after waiting for the disease to progress [5].

If a patient with progressive liver disease can get rid of the virus with the achievement of CBD, the probability of developing complications due to liver cirrhosis and the probability of death due to liver disease is significantly reduced [6].

In Ukraine the triple interferon regimen of antiviral therapy for CHC with pegylated interferons (PEG-IFNα) with ribavirin and sofosbuvir still remains an approved and implemented standard of treatment [6].

The recent rapid development of new antiviral drugs has led to changes in treatment protocols for patients with CHC in accordance with the recommendations, which are constantly, updated AASLD [10]. Different recommendations can be used in different countries, and its cost is a major determinant of management decisions in some countries.

Interferon regimens are no longer recommended in the AASLD guidelines, as direct-acting oral antivirals are currently considered first-line therapy [7].

The components of the drug regimen include:

- daclatasvir + sofosbuvir,
- elbasvir / grazoprevir,
- ledipasvir / sofosbuvir,

• ombitasvir / paritaprevir / ritonavir ± dasabuvir,
• sofosbuvir + simeprevir,
• sofosbuvir / velpatasvir.

The aim of the work is to establish the clinical, laboratory and immunological features of HIV infection on the background of CHC and / or HCV, as well as to compare the effectiveness and safety of interferon-containing and interferon-free HCG therapy in HIV-infected people.

Methods

40 patients with HIV monoinfection (1st group), 77 patients with combined HIV / HCV (2nd group) and another 18 with a combination of HBV, HCV and HIV (3rd group) were under the observation.

All the patients with HCV / HIV coinfection must be prescribed with antiretroviral therapy (ART) with $CD4^+$ lymphocytes <350 cells / ml, regardless of symptoms. The start of treatment was recommended at a $CD4^+$ lymphocyte count of 350-500 cells / ml. Therapy of patients with CHC was carried out using a triple interferon-containing regimen (sofosbuvir 400 mg 1 time per day orally + pegylated interferon alfa-2a at a dose of 180 mcg subcutaneously 1 time per week + ribavirin in dosage depending on weight: 1000 or 1200 mg / day in persons <75 kg or ≥75 kg, respectively), or a pangenotypic combination of direct-acting antiviral drugs - sofosbuvir 400 mg and velpatasvir 100 mg once daily orally. The duration of therapy for both schemes was 12 weeks.

This study was open, non-randomized, retrospective and prospective. The criterion for the effectiveness of HTP was considered to be the achievement of JI. The effectiveness of HCG treatment was analyzed according to current protocols with the determination of HCV HV by PCR in the blood at the 4th and 12th week of the therapy; CBV was determined 12 weeks after HTP.

Results

After analyzing the clinical and laboratory characteristics of patients in these three groups, we found that in HIV monoinfection dyspeptic syndrome was registered in 2,9-3,3 times, and hepatosplenomegaly - in 2,0-2,2 times less often than in the combination of HIV -infections with CHC or with HCV and CHC (in all cases p <0,001).

Among the representatives of all three groups at the time of registration, the 2nd and the 3rd clinical stages of HIV infection predominated (Table 1). Despite the lack of reliability, there is a noticeable tendency to more frequent registration of the 4th clinical stage among HIV-monoinfected - (25,0 ± 6,8) % than in concomitant viral hepatitis - (11,7 ± 3.7) and (16,7 ± 8) , 8)% in the 2nd and the 3rd groups respectively.

All analyzed groups were approximately equivalent in the initial levels of HIV and $CD4^+$ lymphocytes (Table 2). However, among the HIV-infected with concomitant CHC or HCV and CHC were 2,2-2,6 times more likely to register individuals with an initial level of $CD4^+$ lymphocytes <350 cells / ml than among HIV-monoinfected (p <0, 01).

The correlation analysis revealed a medium strength and strong feedback between the indicators of $CD4^+$ lymphocytes and HIV (in patients with HIV only - r = -0,720, p <0, 05; with concomitant CHC - r = -0,763, p <0, 01 with a combination of HCV, CHC and HIV - r = -0,552, p <0,05). It indicates the establishment of a pathological process and the balance between the immune system and the activity of the viral process. This clinical situation is expected and understandable when choosing the tactics of dispensary supervision and the appointment of ART. However, people who have not yet had a manifest manifestation of HIV infection, this

relationship was quite ambiguous. Thus, in some of these patients the level of $CD4^+$ lymphocytes was extremely low (<200 cells / ml), which can hide both true AIDS and reflect the period of seroconversion after a recent infection. Similarly, high HIV rates can reflect both AIDS and recent infections. These discrepancies create inconsistencies not only in establishing the stage of HIV infection, but also in determining the need for ART, which should be addressed in the new Fast Track strategy. According to the ART protocol (2010) [14], some representatives had clear immunological indications (CD4 + lymphocyte level <350 cells / ml) before immediate ART administration, despite the fact that the level of HIV HF was very low (<40 copies RNA / ml). Conversely, some patients had virological indications for ART (HIV> 55,000 RNA copies / ml blood), but their $CD4^+$ lymphocyte levels exceeded 600 cells / ml. Such a collision has already been discussed in the literature [8].

Discussion

In these cases, in our opinion, primarily the immunological basis for the development of AIDS encourages the appointment of ART, despite the fact that there may not be AIDS-indicating diseases or a radical decline in $CD4^+$ lymphocytes, as required by the protocol in 2010. To date, clinical guidelines for the use of ART from the moment of detection of HIV infection [16] which eliminates the shortcomings of the previous protocol.

In the absence of concomitant viral hepatitis, the degree of liver fibrosis on the METAVIR Fo scale was expected to be significantly higher than in HIV / HCV and HIV / HCV / HBV coinfection - (32,5 ± 7,4) % against (7,8 ± 3, 1) and (11,1 ± 7,4) % respectively, and there were no cases of liver cirrhosis at all. The intermediate degrees of liver fibrosis were recorded with approximately the same frequency in all compared groups. The presence of moderate liver fibrosis in the absence of concomitant viral hepatitis can obviously be explained by frequent toxic hepatitis in HIV-infected people due to the use of opioids, alcohol or other substances.

The most common HCV genotype was 1b, which was found in (57, 1 ± 5, 6) and (55, 6 ± 11, 7) % of patients in the 2nd and the 3rd groups respectively. The genotype 3a was established in every fourth to fifth patient, and the genotype could not be identified in (11, 7 ± 3, 7) and (16, 7 ± 8, 8) %. Only in single patients the 2nd genotype of HCV was revealed (tab. 2). A similar ratio is typical for other regions of Ukraine [9]. No correlation was found between the amount of HCV RNA and the genotype of the virus.

22 patients with CHC on the background of HIV infection and 7 people with HCV and CHC in combination with HIV infection, along with ART, also received various treatment regimens for HCV infection. Given the lack of clinical and laboratory differences between these groups, they were combined into one, which was divided into two groups according to the principle of receiving antiviral therapy. For 15 representatives of the first group used triple interferon-containing scheme of antiviral therapy of CHC (sofosbuvir 400 mg 1 time per day orally + pegylated interferon alfa-2a at a dose of 180 mcg subcutaneously + once a week), still used and recommended by modern domestic regulations [9] dosage depending on weight: 1000 or 1200 mg / day in persons <75 kg or ≥75 kg, respectively). The second group consisted of 14 patients who received the last recommended EASL pangenotypic combination of direct-acting antiviral drugs (PPPD) - sofosbuvir 400 mg and velpatasvir 100 mg once daily orally. The duration of therapy for both schemes was 12 weeks.

The main clinical and laboratory characteristics and anamnestic data of patients of both groups before therapy are presented in table 3.

There were no significant differences in the main indicators between the observed groups of patients before the start of CHC therapy. Most of the basic laboratory parameters were within their normal values. Most patients in both groups had moderate liver fibrosis at F2, and one in five had F3. There were no patients with cirrhosis of the liver among the treated persons.

1b genotype HCV was dominant in 10 patients of the 1st group - (66,7 ± 12,2) % and 9 in the 2nd group - (64,3 ± 12,8) %, and in 3 persons of each group established 3a genotype HCV - (20,0 ± 10,3) and (21,4 ± 11,0) %, respectively.

The main characteristics of the effectiveness of the therapy are shown in table 4. In the case of infection with 1b or not typed HCV genotype triple therapy (SOF + PEG-IFNα + RBV) after 1 month provided normalization of aminotransferase activity in 10 of 12 patients (83,3%), and after 12 weeks - in all 100,0% of patients. Instead, the results of HCV viral kinetics in the HTP process lagged behind the dynamics of cytolysis syndrome. Thus, after 4 weeks of treatment, the absence of HCV RNA was found in only 9 people (75,0%), and after 12 weeks - in 10 patients (83,3%). CBV was achieved in 9 patients, because 1 patient with CHC / HIV infection with liver fibrosis F3 on the METAVIR scale had a relapse after successful 12-week therapy, and 2 more people did not immediately respond to the full course of treatment. The results of HTP in the case of infection with HCV genotype 3a were not so impressive. Thus, only one person out of three on the background of this treatment in 4 weeks HCV RNA disappeared from the blood. CBD was later found in 2 of 3 patients. One person did not respond to treatment, although the concentration of HCV RNA in his/her plasma decreased by more than 2 log 10. The dynamics of ALT and AST activity in most cases was parallel to the viral kinetics of HCV. No significant changes in the clinical course of HIV infection in patients of both groups were detected during treatment. Only one patient in the 1st group after 12 weeks of therapy had a recurrence of shingles.

All the patients who received this triple therapy with sofosbuvir, PEGylated interferon α 2 b and ribavirin were able to complete the three-month course, despite the frequent side effects and side effects of the latter two drugs. Thus, almost every person responded to fever, especially after the first injections, signs of asthenovegetative syndrome, weight loss, hair loss and depression. Among the laboratory parameters there were leukopenia, neutropenia and thrombocytopenia. In addition, against the background of interferon therapy in 6 (40, 0%) patients there was a decrease in the absolute number of $CD4^+$ lymphocytes to less than 100 cells / ml. During the treatment, despite the lack of reliability, there is a clear tendency to reduce the median number of $CD4^+$ lymphocytes only in the 1st group of the patients (SOF + PEG-IFNα + RBV) - by 74 cells / ml (p> 0, 05). The dynamics of the level of $CD4^+$ lymphocytes on the background of different schemes of treatment of CHC is presented in table 5. At the same time, the percentage of $CD4^+$ cells did not change significantly. Apparently, the decrease in $CD4^+$ lymphocyte counts was due to the toxic effects of interferon on peripheral blood counts. Twelve weeks after the end of HCV treatment, there was no patient with less than 100 cells / ml of CD4 + lymphocytes, primarily due to antiretroviral therapy given concomitantly with HCG treatment.

Thus, the analysis of the obtained results showed greater efficacy and safety of HCG treatment in HIV patients with pangenotypic combination of PPPD (sofosbuvir and velpatasvir) compared with the triple interferon-containing regimen (sofosbuvir + pegylated interferon C in alba-2a all patients of the 2nd group and only 75, 0% of patients infected with non-3rd genotype HCV – the 1st group. Only with the use of interferon-containing therapy the number of $CD4^+$

lymphocytes was significantly reduced, which, however, did not affect the clinical manifestations of the progression of HIV infection. The tolerability of triple therapy was satisfactory, and the pangenotypic combination of PPPD was good. The occurrence of adverse events in any case did not cause discontinuation of treatment.

1. In HIV monoinfection the dyspeptic syndrome was registered in 2,9-3,3 times, and hepatosplenomegaly - in 2,0-2,2 times less often than in the combination of HIV infection with CHC or with HCV and CHC (p <0,001). Among HIV / HCV- and HIV / HCV / HBV-co-infected, individuals with an initial level of $CD4^+$ lymphocytes <350 cells / ml were registered 2,2-2,6 times more often than among HIV-monoinfected (p <0,01).

2. The average strength and strong feedback between the indicators of $CD4^+$ lymphocytes and HIV (in patients with HIV only - r = -0,720, p <0, 05; with concomitant CHC - r = -0,763, p < 0, 01, with a combination of HCV, CHC and HIV - r = -0,552, p <0,05). It indicates the establishment of a pathological process and the balance between the immune system and the activity of the viral process.

3. In the absence of concomitant viral hepatitis, the degree of liver fibrosis on the METAVIR F0 scale was determined significantly more often than in HIV / HCV and HIV / HCV / HBV coinfection, and there were no cases of liver cirrhosis at all.

4. In our study the ratio of HCV genotypes was similar with other regions of Ukraine: dominated by 1b, every fourth or fifth patient was diagnosed with genotype 3a, less often it could not be identified and only in single patients genotype 2 HCV was detected.

5. In the case of infection with 1b or not typed HCV genotype, triple therapy after 1 month provided normalization of aminotransferase activity in 83,3% of patients, and after 12 weeks – in all patients. Instead, the results of HCV viral kinetics in the HTP process lagged behind the dynamics of cytolysis syndrome. SVR was achieved in 75, 0% of such patients, and in the case of infection with the 3a genotype HCV - in 2 of 3 people. The dynamics of ALT and AST activity in most cases was parallel to the viral kinetics of HCV.

6. Adverse events and side effects of the therapy are noted only in the process of HCG treatment according to the interferon-containing three-component scheme: hyperthermia, general malaise, anorexia, weight loss, depression, decrease in leukocytes and lymphocytes and consequent decrease in absolute blood CD4 + lymphocytes, the percentage of cells did not change.

7. Therapy with sofosbuvir + velpatasvir proved to be much more effective and safer: CBV was found in 100, 0% of patients with HIV / CHC in non-HCV genotype 3 and in 2 of 3 patients infected with HCV genotype 3a. The concentration of aminotransferases even in the absence of CBR did not exceed VMN. The patients tolerated this treatment well, only in isolated cases there were noting moderate headache, fatigue and nausea, which could be due to other reasons.

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