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EVALUATION OF THE EFFICACY OF ANTIVIRUS DRUGS IN CHRONIC DELTA HEPATITIS

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Annotation
The value of efficiency of PEG-IFN-alfa 2-b Algeron was represented in combination with the analogy of nucleoside Tenofovir alafenamide (TAF) in therapy of CHDV during 6 months in 50 patients. The diagnosis of the disease was determined through revealing markers of hepatitis B and hepatitis D – HbsAg, HBV-DNA, anti- delta, HDV-RNA in ELISA and PCR in patients. The activeness of pathological process in liver was revealed with the help of aminotransferases test. The stage of illness was established through liver Fibro scanning. Algeron was prescribed in dose of 1,5 mcg/kg/week in combination with TAF in 25 mg/day. The efficiency of this scheme was tested after 4 injections (after 1 month from the beginning of the treatment), then after 3 and 6 months. The second group of 30 patients with same diagnosis were given TAF with 25 mg/day for 2 years. After 3 and 6 months from the beginning of the therapy the viral load (VL) of delta virus was examined. Significant decreases of VL were established in all periods of observation. After 3 months HDV in 28,9 of patients became undetectable. Other percentage of patients had deceased VL (2000-3000 IU/mg), but it did not disappear. Because of decrease of VL the level of aminotransferases and the level of fibrosis decreased respectively. Long-term use of the given scheme of therapy is more appropriate. In the second group of patients TAF monotherapy caused insignificant decrease of BH, often increasing in 3 months, then, small decline of BP is noted to the 6th month of the therapy. This is apparently - self healing, rather than TAF effect.

Keyswords: CHD, diagnosis, Algeron, Tenofovir alafenamide (TAF), viral load, therapy efficiency, side effects.

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ОЦЕНКА ЭФФЕКТИВНОСТИ ПРОТИВОВИРУСНЫХ ПРЕПАРАТОВ ПРИ ХРОНИЧЕСКОМ ГЕПАТИТЕ ДЕЛЬТА

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Аннотатция.
Представлены результаты ПЭГ-ИФА-альфа 2-в – Альгерон в комбинации с нуклеозидным аналогом Тенофовир алафенамид (ТАФ) в терапии ХВДГ в течение 6 месяцев у 50 больных (основная группа). Диагноз заболевания устанавливался на основании выявления у больных маркеров гепатита В и гепатита Д – HbsAg, HBV-DNA, анти-дельта, HDV-RNA в ИФА и ПЦР. Активность патологического процесса в печени выявляли при помощи анализа аминотрансферазы. Стадия заболевания устанавливалась при помощи Фибросканирования печени. Альгерон назначался в дозе 1,5 мкг/кг/ неделю в комбинации с ТАФ по 25 мг/сутки. Эффективность данной схемы контролировалась после 4 инъекций (через 1 мес от начала лечения), а затем через 3 и 6 месяцев. Во второй (контрольной) группе 30 больным с тем же диагнозом назначали нуклеозидный аналог ТАФ по 25 мг в сутки (1 таблетка) на 2 года. В сроки через 3 и 6 месяцев от начала терапии контролировали вирусную нагрузку (ВН) дельта вируса. Установлено выраженное снижение ВН в основной группе во все сроки наблюдения. У 28,9% пациентов через 3 мес HDV стал не определяемым. У остальных больных ВН снизилась до 2000-3000 МЕ/мл, но не исчезла. Соответственно понижению ВН снижались уровни аминотрансфераз и уменьшался степень фиброза. Целесообразно более длительное применение данной схемы терапии. Во 2 группе больных монотерапия ТАФ привела к несущественному снижение ВН, нередко нарастая через 3 мес от начала терапии, затем, к 6 месяцу отмечено небольшое снижение ВР. Это, по-видимому, можно объяснить естественными процессами самоизлечения, чем эффект ТАФ.

Ключевые слова: ХДГ,диагностика, лечение, Альгерон, Тенофовир алафенамид, вирусная нагрузка , эффективность терапии, побочные явления.

Relevance
One of the most important problems of hepatology is the antiviral treatment of chronic delta hepatitis (CDH). This problem remains open despite the fact that it has

been almost 45 years since the discovery of delta virus [1,7]. The main reason for this is that the delta virus is defective, it gets its coat only with the help of the surface antigen of the hepatitis V virus - HbsAg - and can easily enter hepatocytes. In addition, the delta virus does not contain special enzymes that act on antiviral drugs [7,11]. Therefore, in recent years, it has been an important issue to develop drugs that resist the entry of the delta virus into the cell, rather than killing the virus. At the same time, other problems of SDG, that is, the structure of the virus, replication processes [11-13], epidemiology of the disease [2,3], pathogenesis and clinical course have mostly been solved [1,4,6,7].

It is known that delta hepatitis (DG) occurs in 2 variants: variant 1 - co-infection (acute hepatitis V + acute hepatitis delta) - in this case, the disease passes in a severe or very severe form, and a large percentage ends with acute hepatic encephalopathy (AHE) [1,6 ,7]; Option 2 - when a patient with HBsAg carrier or chronic viral hepatitis V is infected with delta virus, this patient develops rapidly progressive chronic liver disease, leading to liver cirrhosis in a very large percentage [1,4,6]. It can be definitely stated that there is no such rapidly developing disease among other liver diseases.

Treatment of SDG with various antiviral drugs, including nucleoside analogs, has not shown significant antiviral effect [4,6,10,16]. At the same time, the use of interferon drugs, especially pegylated (PEG-IFN) interferons for 24-48 weeks, resulted in virological and biochemical results in 27-47% of patients [8-10,14,16]. However, 6 months after stopping treatment, the majority of patients experienced viral recurrence [6,14].

Algeron, a drug belonging to the group of pegylated interferons developed in the Russian Federation, played an important role in the treatment of hepatitis C until 2015 [5]. However, with the arrival of new antiviral drugs on the market for the treatment of hepatitis C, the importance of Algeron in the treatment of hepatitis C has disappeared.

It should be noted that interferons have a non-specific antiviral effect, which means that regardless of which virus it is, they will in most cases reduce or lose their activity under the influence of interferons.

Purpose of work

Evaluation of the virological effect of pegylated interferon alfa-2v (cepeginterferon "Algeron") and nucleoside analogues Tenofovir alafenamide in patients with SDG.

Research Materials and Methods

Virological, biochemical and liver elasticity levels of Algeron were studied in 50 patients with SDG. The diagnosis of SDG is based on the anamnesis of the patients (previous VGV), the subsequent detection of the delta virus, the clinical course of the disease, serological markers - HBsAg, HBV-DNA +/-, anti-delta and HDV positivity in the blood, increased aminotransferases to varying degrees, increased elasticity of the liver on the Fibroscan machine. was placed. The following guidelines were followed for treatment with this drug: HBV-DNA-PTsR positive/negative, HDV-RNA-PTsR-positive, high liver function tests and fibrosis 1-2 or higher on Fibroscan. Algeron drug was recommended to patients at a dose of 1.5 μg/kg, once a week, subcutaneously, for 24 weeks. Tenofovir alafenamide, a nucleoside analog, was prescribed to patients at 25 mg/day for at least 2 years. Indications and contraindications for treatment with this scheme were analyzed in patients. Patients were not included in this group if they had various decompensated diseases, including sub-decompensated cirrhosis of the liver. Follow-up of patients was carried out in the following periods: after the start of treatment, after 4 injections, i.e. after 1 month, the examination during this period was to determine whether the patient had a rapid virological response (RVR), the next examination - after the start of treatment, after 3 months (after 12 injections - i.e. to detect early virologic response (EJ), the follow-up examination was performed at the end of treatment, i.e. after 6 months. Group 2 patients (control group) - 30 patients, who mainly received Tenofovir alafenamide, which belongs to the group of nucleoside analogues, at 25 mg/day. Both groups of patients were prescribed hepatoprotectors and Liverin, a drug belonging to the group of antifibrotic drugs. Patients in the control group were also examined at 3.6 months after the start of treatment.

Inspection Results

Patients generally did not tolerate Algeron poorly, meaning that no patient discontinued the drug due to an adverse effect. In addition, some side effects, which are very typical for interferons, were observed in patients. The most common side effect is a flu-like condition, which was expressed in patients with varying degrees of chills, pain in the limbs and body in general, increased body temperature, headache, loss of appetite, and in some cases, nausea. These symptoms were especially strong after the first injection, and this condition decreased sharply in patients after the second, especially after, injections. It should be said that after 4 injections (after 1 month after the start of treatment), a decrease in the number of platelets was observed in most patients, although this effect developed more strongly after 3 months, that is,

after 12 injections. In some patients, in order to increase platelets, Algeron was temporarily stopped or platelet-increasing drugs - Trombopag (Revoleyd, Elbonix) were used.

Patients were divided by age and gender as follows. Not a single patient aged 16-20 years was found. The absence of patients at this age can be assessed as the introduction of vaccination against viral hepatitis V, which began in 2000. The age of patients is mainly between 21-50 years old, 7 patients aged 21-30 (14.0%), 14 patients aged 31-40 (28.0%), and 12 patients aged 41-50 (24.0%)) established. It is correct to associate the large number of patients in these groups with the very high rates of the disease in the years 1970-2000. The higher frequency of the disease in men can be explained by the data presented in the literature, that is, the genetic weakness of men in relation to viral GV, the development of HBsAg-carriage in them, as well as the higher possibility of delta virus infection. In the control group, the distribution of patients by age and gender was similar to the patients of group 1.

The dynamics of delta virus load (VU) (HDV-RNA-PTsR-quantity) in both groups of patients showed an average VUu level of 8,777,840 ME (8.7x10 6)) before the start of treatment, that is, a very high indicator. After the start of the treatment, after 4 injections VU decreased to 263876 ME (2.6x10 5) R. 4 Patients were not excluded from the study even if they did not have a decrease in VU after the injection, because not all patients may not have a decrease in VU at 1 month. Therefore, they were recommended to continue treatment and to check VUu after 8 injections (after 2 months). During the 3-month period after the start of the treatment, delta VU decreased again significantly - up to 31987 ME (3.1x10 4) (R). During this period, in patients whose HDV-RNA-PTsR did not decrease, or, on the contrary, increased, in other words, in cases of virological failure, Algeron was stopped, and patients continued Tenofovir alafenamide 25 mg/day. Such patients accounted for 5/50, i.e. 10.0%. The follow-up examination of patients in the group of those who continued the treatment was carried out after 6 months - (after 24 injections), that is, at the end of the treatment. The average value of HDV-RNA-PTsR during this period decreased to 3989 ME/ml (3.9x10 3 copies of HDV/ml). It should be noted that 9 (20.0%) of this group of patients had a negative HDV-RNA-PTsR after 3 months, and 4 (8.9%) had a negative result after 6 months (after 24 injections), i.e. was observed until the end of the treatment. Thus, the number of people who got a negative result was 13 people (28.9%). It should be noted that the majority of patients with a negative result after 3 months had a relatively low initial viral load (3000-10000 ME/ml). Therefore, patients with a relatively low viral load can be included in the successful group from the point of view of treatment prediction.

The dynamics of HDV viral load in patients receiving tenofovir alafenamide monotherapy (control group) also in this group, the mean value of VU before the start of treatment was 5104626 (5.1x10 6 ME/ml). In contrast to group 1, patients in this group were not followed up after 1 month because 1 month of treatment is too short a period for tenofovir alafenamide and it is not reasonable to have a virological response during this period. Therefore, patients were examined 3 months after the start of treatment. The average viral load during this period was 492176 -4.9x10 5 ME/ml, and after 6 months it was 47677 - 4.7x10 4 . Comparison of the viral load in both groups shows that this indicator reliably decreases in group 1 patients. The relative reduction of the viral load in group 2 patients can be attributed mainly to the natural processes of recovery, as well as hepatoprotectors and antifibrotic drugs taken by the patients.

Summary

1. The combination of Algeron and Tenofovir alafenamide for 6 months (24 weeks) gives a positive result, and it is appropriate to use this drug as a virological treatment.
2. In the course of treatment, side effects typical for interferons are observed, but they cannot be a reason for stopping the drug. The most common side effect is a flu-like syndrome.
3. Long-term use of Algeron drug, i.e. for 1 year (48 weeks), is appropriate, because when patients were treated for 6 months, the viral load decreased to 2000-3000 ME/ml in most cases, but a negative result was achieved in only 28.9%.

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