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ABSTRACT

of the thesis for the degree of Doctor of Philosophy

COMPARATIVE COMPLEX EVALUATİON OF MODERN PROGRAMS OF ANTIVIRAL TREATMENT FOR PATIENTS WITH HEPATITIS B AND C

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ACTUALITY OF THE RESEARCH.

The first drug recommended for antiviral therapy (AT) in patients with chronic hepatitis B (CHB) was human interferon (IFN). Since 1985, injectable recombinant interferon (r-IFN) has been used for AT in patients with CHC. Since 1990, r-IFN drugs have also been used for the AT of patients with Chronic Hepatitis C (CHC) [1,2].

The use of r-IFN drugs has led to achieving the recovery of both a certain part of CHC and CHB patients (since the late 1990s, r-IFN was prescribed in combination with ribavirin). However, the use of r-IFN drugs was limited to several contraindications, and long-term use was accompanied by side effects. Thus, the search for improvement of the AT methods continued.

In 1999-2000, "PEG-IFN" drugs were discovered, which are characterized by higher efficacy, lower reagent and ease of use. These drugs soon "replaced" r-IFN drugs in AT programs of both the CHB and CHC. However, their inclusion in practice has at least doubled the cost of AT for patients and reduced their widespread use among patients[3,4]. The beginning of the XXI century, along with r-IFN and PEG-IFN drugs, oral antiviral drugs based on nucleoside analogues (NA) began to be used to treat patients with CHB.

Their appointment for a period of one to several years led to an increase in the price of the AT and limited use. In 2013, the introduction of DAAD (direct-acting antiviral drugs) based on a "virus protease inhibitor" for the AT of CHB patients began, which led to an increase in treatment options and a decrease in the number of contraindications to therapy. However, at the same time, the rise in

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1. Ершов Ф.И., Киселев О.И. Интерфероны и их индукторы. М.: ГЭОТАР-Медиа, 2015, -466 с.

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3. Мамедов М.К., Кадырова А.А. Интерфероны и их применение в клинической медицине. М.: Кристалл, 2005, -288 с.

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However, according to the official position of the WHO on social policy in the field of treatment of patients with CHC and CHB, the strategic policy of AT financing for each country should be based on the real economic potential of the country and should be based primarily on the availability of the majority of the population. It is clear that in countries with limited budgets, this policy should be aimed at making it accessible to the general population, even if it is not the most effective.[5]

Given the above, we must note that in developed countries with different levels of economy and public health, the issue of the implementation of various programs of the WHO for the treatment of patients with CHB and CHC is not fully resolved. It is not possible to make an objective comparison of the existing treatment programs for patients with CHB and CHC only based on the breadth of application, therapeutic efficacy and the characteristics of side effects. In addressing this issue, economic indicators such as price and accessibility among the general population in countries with limited budgets should be taken into account in the first place. This situation prompted us to conduct the current study.

PURPOSE OF THE RESEARCH. The aim of the research was to identify and compare the therapeutic efficacy and side effects in the use of various antiviral drugs in patients with CHB and CHC in clinical observations, as well as to assess the economic feasibility.

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6. WHO global hepatitis programme. Prevention and control of viral hepatitis infection: intern strategy for global action 2012 -2014. WHO: Geneve, 2013, 58 p.;

7. WHO Guidelines for the screening, care and treatment of person with hepatitis C infection (updated version). Geneva, 2016, 132 p.

8. WHO Hepatitis B treatment workshop. Geneve, 2010, 36 p.

RESEARCH TASKS.

1. To determine the therapeutic efficacy of drugs based on recombinant, pegylated interferon and nucleoside analogues (NA) used to treat patients with CHB and compare them with similar indicators.

2. To assess the appropriateness of the consistent use of interferon drugs and drugs based on nucleoside analogues in the treatment of patients with CHBand to determine the therapeutic efficacy of this treatment.

3. To determine and compare the combined use of recombinant, pegylated interferon drugs with ribavirin and the therapeutic efficacy of various drugs based on inhibitors of viral enzymes in the treatment of patients with CHC.

4. Comparison of the nature, frequency and manifestations of side effects of antiviral drugs used in the treatment of patients with CHB and CHC.

SCIENTIFIC SIGNIFICANCE OF RESEARCH RESULTS. The results of various AT programs, including recombinant and pegylated IFNs and pill-type drugs (nucleoside analogues (NA) in the treatment of CHB and inhibitors of viral enzymes in the treatment of CHC patients), were retrospectively analyzed from the same clinical-laboratory observation, laboratory base and methodological position and prospectively identified and compared. When using r-IFN drugs for the treatment of both CHB and CHC patients, the choice of the optimal dose for each patient was shown. By increasing their dose, it is possible to obtain the frequency of treatment effectiveness following the effects obtained with the use of PEG-IFN drugs. By reducing the dose of r-IFN drugs, it is possible to reduce the incidence of side effects of AT and reduce the incidence.

Using adequate monitoring of antiviral drug side effects, the author showed that the spectrum, frequency, and severity of most side effects of r-IFN in both CHB and CHC patients from the similar effects of PEG-IFN does not have differed statistics. It was also

noted that the nature and manifestations of the immunotropic effects of PEG-IFN drugs did not differ significantly from the analogues of r-IFN drugs.

Calculations have been made that the cost of a course of AT treated with original r-IFN drugs in patients with CHB and CHC is at least twice lower than the cost of similar therapy with original PEG-IFN drugs. In addition, if the AT is treated with generic r-IFN drugs, then the cost of treatment will be 3-4 times lower than the cost of treatment with PEG-IFN drugs.

PRACTICAL VALUE OF RESEARCH.

Summarizing the results, the author concluded that in the treatment of patients with CHB and CHC, r-IFN drugs can be used, which are partially behind the effect of PEG-IFN, but economically incomparable. Based on the nucleoside analogues used to treat patients with CHB, it is recommended to prescribe the drug only to patients who are contraindicated in the use of IFN drugs and previously treated with PEG-IFN drugs is not effective enough. Finally, from an economic point of view, it has been established that DAAD, which is based on viral enzyme inhibitors, should be used to treat patients with CHC who have previously been treated with PEG-IFN.

Given the above, r-IFN drugs can be used in the treatment of patients with CHB and CHC as before. Thus, the therapeutic effect obtained in this case will be partially low the effect obtained during the use of PEG-IFN drugs.

PRINCIPLES PRESENTED FOR DEFENS

1. PEG-IFN drugs can be considered as the main tool in the treatment of patients with primary CHB, as well as as a useful tool in the treatment of patients with CHC (in combination with ribavirin) without contraindications.

2. r-IFN drugs, which are comparable in effectiveness and side effects to PEG-IFN drugs, can be considered as more economically accessible analogues of PEG-IFN drugs.

3. In the limited economic opportunities to finance the treatment of patients with chronic viral hepatitis, r-IFN drugs can be used in the treatment of patients with CBH and certain groups of patients with CHC.

PUBLISHING AND IMPLEMENTED THE EXPERIENCE THE RESULTS. The important theoretical conditions underlying the work and the main results of scientific research are reflected in 20 journal articles published in Azerbaijan and 5 scientific journals published in Russia, Belarus, Ukraine and Kazakhstan.

The main results of this study were included in the methodological recommendations approved by the Board of the Ministry of Health of the Republic of Azerbaijan in 2015 and 2016.

APPROBATION OF WORK.

The results of this research were presented and discussed at 4 scientific-practical conferences in Baku (2014, 2015, 2016) as well as at seminars organized by the Ministry of Health of the Republic of Azerbaijan for practicing doctors.

Approval of the finished dissertation took place at the scientific seminar One-time dissertation council BFD 2.28 under Dissertation Council FD 2.28 of Azerbaijan Medical University in 30.03.2021

VOLUME AND STRUCTURE OF THE WORK.

The dissertation is published in the form of a 154-page text and consists of a literature review, 5 chapters of personal research, a summary, conclusions and a list of references. The latter covers 150 cases, 80 of which are in foreign languages. The dissertation is illustrated with 35 tables.

CLINICAL MATERIALS AND RESEARCH METHODS. Used in the course of the work: 1) materials obtained during retrospective analysis of archival data of patients with CHB and CHC previously receiving AT, and 2) materials obtained during prospective observation of patients with CHB and CHC receiving AT with the participation of the author.

Data about patients with CHB and CHC who received AT from two medical institutions, the Gastroenterology Department of the Central Hospital of Oilworkers (CHO) in 2001-2010 and the Clinical Virology Department of the N. Tusi Clinic in 2006-2015.

Prospective researches were conducted during 2011-2016 in the outpatient department of the CHO polyclinic department as an outpatient in 543 patients with CHB and CHC who received AT with various programs. Number of patients under observation: 324 patients with CHB and 219 patients with CHC.

In the course of these observations, patients were prescribed thymosin-alpha1 and ribavirin (RV) in the form of r-IFN (ukraferon) and PEG-IFN (pegasys), as well as ZD (zadaxine). Besides, lamivudine (LAM), telbivudine (TEL) and entecavir (ENT) were used to treat CHB patients, boceprevir (BOC), telaprevir (TVR) and sofosbuvir (SOF) were used to treat CHC patients. All drugs are prescribed in standard doses.

The results of laboratory tests used in the present study were conducted in the Immunology Laboratory of the Scientific Research Institute of Hematology and Transfusiology named after B.N. Eyvazov (Baku).

Recent efficacy indicators for the therapeutic efficacy of AT in both CHB and CHC patients have been established. The main indicator of efficacy was the frequency of recording of “sustained virological response” (SVR), which was determined by the absence of HBV DNA or HCV RNA in the patient's blood 6 months after the end of treatment.

The obtained results were mathematically processed using the computer program “STATISTICA 6”.

TREATMENT OF CHB PATIENTS. In assessing the effectiveness of r-IFN drugs, the results of treatment of 213 patients with r-IFN with various r-IFN drugs for 24 weeks under the "3 injections per week" program were analyzed retrospectively.

Patients with CHB with 3 or more Curabelic predicates received a single dose of 3 million IU r-IFN (intron A or reaferon). Their SVR

registration frequency was 29.0 ± 4.0%. The second group of patients with a lower chance of recovery received intron A or roferon A at a dose of 5-6 million IU. Their SVR registration frequency reached 43.9 ± 5.5%. The SVR level of patients in both groups was independent of the r-IFN being treated. At the same time, with increasing the dose of the injected drug r-IFN, it was observed that the therapeutic effect of patients with CHB increases.

We also conducted a prospective follow-up of 98 patients with ukraferon (UKR), one of the generic r-IFN drugs, treated for 3 weeks in a "3 injections per week" regimen. UKR was given to patients by the Ministry of Health. 68 patients with 3 or more predictors of curability were prescribed ukraferon at a dose of 3 million IU, and other patients with fewer predicators were prescribed ukraferon at a dose of 5 million IU. However, in patients receiving 9 million IU and 15 million IU per week, the SVR registration frequency was 29.4 ± 5.5% and 33.3 ± 8.6%, respectively. As a result, the SVR recording frequency reported in patients receiving UKR did not differ significantly from that in patients receiving intron A, roferon A, or reaferon. This meant that the treatment effect of ukraferon with the AT effect was comparable to that of the original r-IFN drugs [1,7].

The therapeutic efficacy of PEG-IFNs was assessed through a retrospective analysis of materials presented to us on 78 patients with CHB (including 22 patients with HBeAg-negative CHB). They received a single dose of 180 mcg in a single-injection weekly monotherapy regimen with pegasis for 24 weeks. The recorded SVR frequency of these patients was 33.3 ± 5.3%. Given that these indicators do not differ significantly from similar indicators when using r-IFN, it can be assumed that the use of r-IFN drugs instead of PEG-IFN in the treatment of patients with CHB did not provide a significant increase in the therapeutic effect.

In a prospective follow-up, we evaluated the efficacy of ATs in 128 CHB patients treated with 3 PEG-IFNs: pegintron (150 mcg dose), pegasys, and pegaferon (both 180 mcg dose). All drugs were injected once a week. Although the therapeutic effect in these

patients did not depend on which of the PEG-IFN drugs used for treatment, the reported SVR level was 44.5 ± 4.4% [3,7,8].

Thus, the SVR level in patients receiving PEG-IFN was slightly higher than the SVR level in patients receiving r-IFN at standard doses. At the same time, the incidence of SVR in these patients did not differ significantly from that of patients receiving with higher doses of r-IFN. These data suggest that r-IFN drugs can be used to treat patients with AT, along with PEG-IFN drugs. The efficacy of the latter at increased doses did not differ from the efficacy of treatment with PEG-IFN [9,21].

To assess the effectiveness of combined AT programs in patients with CHB, SVR was prescribed during 2 weeks in the application of 2 combined programs: 1) injection of PEG-IFN + oral LAM and 2) injection of PEG-IFN + ZD.

The PEG-IFN + LAM program was used to treat 47 patients (including 15 patients with HBeAg-negative CHB) who have prescribed 100 mg of LAM daily in addition to pegasis injections. According to the results, the SVR registration frequency was 42.6 ± 7.1%. It was concluded that this AT program was not superior to the standard AT program in pegasus monotherapy [18, 28].

The PEG-IFN + ZD program was used to treat 51 patients (including 16 patients with HBeAg-negative CHB). In addition to Pegasys, they were injected with 1.6 mg of ZD solution twice a week. As a result, the SVR registration frequency was 58.8 ± 6.8%, which was higher than that of patients receiving AT under the PEG-IFN + LAM program. It has been shown that this program is more effective, especially in patients with HBeAg-negative CHB, and that this program should be preferred during AT [12].

Because the comparative efficacy of nucleoside analogues in the treatment of patients with CHB has not been fully evaluated, we retrospectively analyzed the use of 3 of these drugs (LAM, TEL, and ENT) in 86 patients with CHB. They were prescribed LAM (100 mg per day for 35 patients), TEL (100 mg per day for 28 patients) or ENT (0.5 mg per day for 23 patients) for 18 months. It was found that the frequency of SVR registration in patients receiving LAM -

68.6%; In patients receiving TEL - 86.7%; In patients receiving ENT - 86.9%. TEL and ENT showed approximately the same efficiency, significantly exceeding LAM efficiency. This and the low induction rate of drug resistance characteristic of them have made it possible to recommend the treatment of CHB patients with the above-mentioned drugs as first-line drugs that have contraindications to IFN drugs or do not give the expected results of previous treatment with IFN drugs.

Finally, we evaluated the results of the consistent application of both strategies in the treatment of patients with CHB. The endpoint efficacy of AT was assessed in patients with CHB who were initially treated with PEG-IFN drugs ("first" strategy) and then treated with one of the nucleoside-based drugs ("second" strategy) after no effect was determined [19,31] .

128 patients with CHB who were previously treated with one of the PEG-IFN drugs for 6 months, 71 patients who did not respond to the treatment were isolated. 35 of them - LAM, 28 - TEL and 8 - ENT. Such treatment was carried out for 18 months. Six months after the end of therapy, the SVR recording frequency was found to be 80% in patients receiving LAM, 96.4% in patients receiving TEL, and 100% in patients receiving ENT. In other words, SVR (88.7%) was noted in 63 of the 71 patients who did not receive the expected results with IFN drugs during treatment. Thus, with the consistent application of both "strategies", we found that 120 out of 128 patients with CHB were provided with SVR, which was 93.7%. This meant that the AT, which consistently used both strategies in patients with CHB, was able to obtain SVR in the majority of these patients.

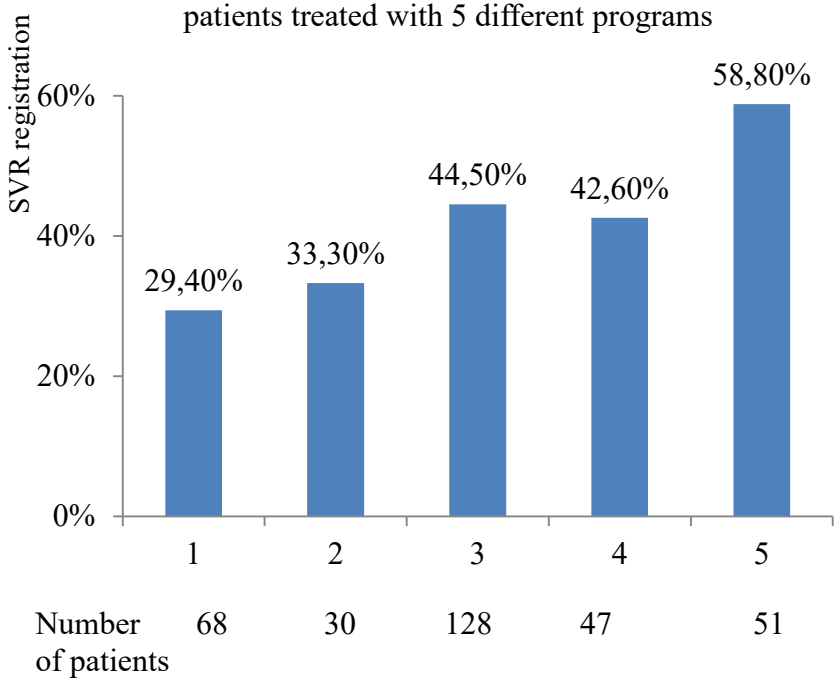
We also took into account the official position of the WHO when choosing the optimal approach to the treatment of patients with CHB. According to this position, each country should take into account the following in the financing policy of the AT: 1) it should be based on the economic potential of the country and 2) it should focus on the use of treatment methods that are more accessible to the general population. It is clear that this policy is not more effective in

the context of a limited budget, but it is primarily accessible to the general population [23].

It is clear that two recommendations need to be followed. First and foremost, use more affordable drugs that provide healing to at least some patients and do not require antiviral therapy in the future. Second, such expensive drugs should be used in patients who have contraindications to treatment with IFN drugs or who are ineffective in prescribing them. This means that first the first "strategy" should be set by the AT, then the second "strategy".

The main indicators of the effectiveness of treatment of patients with CHB using various drugs, identified in prospective observations, are presented in the graph described in Graph 1 below.

Graph 1. SVR registration frequency in 324 CHB patients treated with 5 different programs



1 - UKR in a single dose of 3 million IU

4 - PEG-IFN + LAM

2 - UKR in a single dose of 5 million IU 5 - PEG-IFN + ZD
3 - PEG-IFN

TREATMENT OF CHC PATIENTS. Initially, we retrospectively evaluated the effectiveness of the r-IFN + RV program in 237 CHC patients of both sexes (as well as 138 CHC patients with genotype 1) using r-IFN drugs - intron A and roferon A. These patients were prescribed 3 injections per week, r-IFN at a dose of 3-5 million IU and RV at a dose of 800-1000 mg daily under the AT program. Treatment was 48 weeks in patients with CHC caused by genotype 1 HCV and 24 weeks in patients with CHC caused by other genotypes HCV. The incidence of SVR in these patients averaged 52.6 + 3.2% in patients with CHC caused by genotype 1 HCV, and 61.2 + 4.9% in patients with CHC caused by other genotypes HCV. It is clear that the latter was higher than the first ($p < 0.05$). This suggests that the effectiveness of this AT program is lower in patients with CHC caused by genotype 1 HCV.

Then we participated in the prospective observation of 43 CHC patients who received AT under the "r-IFN + RV" program. UKR at a dose of 3 million IU was used as r-IFN drugs in these patients. The average incidence of SVR was 46.5 + 7.6%, in patients with CHC caused by genotype 1 HCV was 39.1 + 10.1%, and in patients with CHC caused by other genotypes HCV was 55.0 + 11,1% [2,24]. It should be noted that the difference between the SVR registration frequency in patients treated with UKR and the same indicator in patients treated with intron A or roferon A was not accurate.

We also explored the possibility of increasing the effectiveness of this program by increasing the UKR dose to 6 million IU against a standard dose of RV. Following this observation in 39 patients, we found that the mean incidence of SVR was 53.8 + 8.0% and significantly exceeded SVR in patients receiving UKR at a dose of 3 million IU. The prevalence of SVR in patients with CHC caused by genotype 1 HCV was 47.6 + 11%, significantly increasing the similarity in patients treated with lower-dose UKR. The incidence of SVR in CHC patients with other genotypes caused by HCV was 61.1%. These findings suggest that the use of “high-dose” AT

programs in CHC patients increased the SVR registration rate reported in CHC patients, primarily caused by genotype 1 HCV [11].

We began evaluating the effectiveness of the PEG-IFN + RV AT program by retrospectively analyzing data on the AT results of more than three hundred CHC patients previously monitored by doctors in the Central Hospital of Oilworker gastroenterology department. According to the results of these data, the average incidence of SVR was 63.8%, in patients with CHC caused by genotype 1 HCV - 56.3%, and in patients with CHC caused by other genotype HCV - 76.8%. These data showed that the treatment of patients with CHC under the program, which included pegasys, was more noticeable during treatment with programs that included r-IFN drugs.

Then we participated in a prospective observation using the PEG-IFN + RV treatment program to treat 69 CHC patients (47 of whom were genotype 1 HCV-induced CHC patients). It turned out that the average frequency of SVR was 55.0 + 6.0%. In patients with CHC caused by genotype 1 HCV, it was 48.9 + 7.3%, and in patients with CHC caused by other genotype HCV was 68.2 + 9.9% [10,23]. In addition, in a study of 47 CHC patients induced by genotype 1 HCV, we identified a polymorphism variant of the interleukin 28b gene (IL28b) in them and compared SVR levels in these patients upon completion of the observation.

It was found that SVR was recorded in 87.5% of patients with CC-variant of this gene, and SVR frequency was recorded in patients with CT- or TT-variant, respectively, at 45.4 and 16.6%, respectively. As can be seen, higher levels of SVR were higher in the CC variant of polymorphism of the IL28b gene, and lower rates were found in the TT variant of polymorphism of the same gene.

We also observed the treatment of 47 CHC patients of both sexes (including 27 CHC patients with genotype 1 HCV) under the peqasys + ZD (instead of RV) program. These patients were prescribed pegasys injection in "1 injection per week" mode and ZD injection in 1.6 mg dose in "2 injections per week" mode. However, the average frequency of SVR was 66.0 + 6.9%. Genotype 1 was 59.3 + 9.5% in patients with CHC caused by HCV, and 75.0 + 9.7%

in patients with CHC caused by other genotype HCV. Taking into account all these results, we decided that the effectiveness of the "pegasys + ZD" program, at least, does not lag behind the "pegasys + RV" treatment program [12].

Finally, we summarized our experience of using one of the three DAADs - BOC, TVR and SOF - as the third component of CHC treatment programs. Such treatment was prescribed to patients with a low chance of pre-treatment with the PEG-IFN + RV program (genotype 1 HCV and TT variant of the IL28b gene).

Thus, 3 patients received therapy for 48 weeks under the program "PEG-IFN + RV + BOC" (BOC was prescribed in a single dose of 2.4 g). The incidence of SVR in these patients was 66.6% [15,16].

6 patients received therapy for 48 weeks under the program "PEG-IFN + RV + TVR" (the latter was prescribed in a single dose of 2.25 g). The incidence of SVR in these patients was 83.3% [15,16].

Twelve patients received therapy for 12 weeks under the PEG-IFN + RV + SOF program (SOF was prescribed in a single dose of 400 mg). It was found that the frequency of SVR registration in these patients reached 91.7%. These results showed that treatment of CHC patients with one of the 3-component programs, which included inhibitors of viral enzymes, was more effective in all cases than the standard 2-component program. However, PEG-IFN + RV + SOF was the most effective treatment program, including one for DAAD [5,15,16].

The main indicators of the effectiveness of treatment of patients with CHC using various programs identified in prospective observations are shown in the graph described in Graph 2.

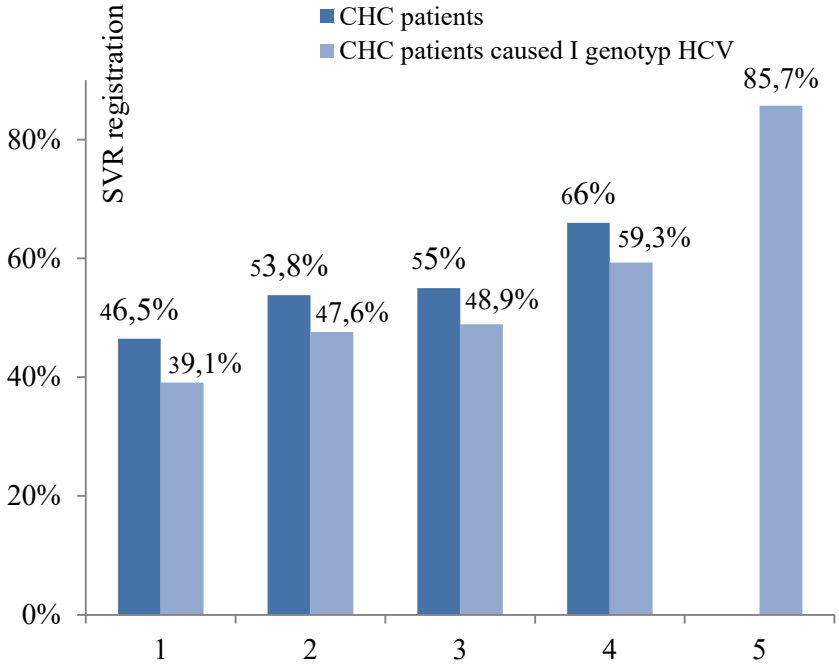
In addressing the optimal choice of AT programs for patients with CHC, we took into account the funding policy of the WHO' for the treatment of both CHB and CHC patients. Comparing the effectiveness, economic feasibility and justification of the widespread use of these treatment programs in patients with CHC, we concluded that r-IFN drugs can be an economically viable alternative to PEG-IFN drugs [21,25].

In this case, the effect is partially behind the effect of PEG-IFN. Given the above, it is advisable to follow the following two recommendations.

The first is to use drugs that are more accessible to patients who are able to provide recovery to at least some of their patients and who do not need antiviral therapy in the future.

Second, treatment with DAAD should be given only to patients who have contraindications to IFN drugs, and their previous therapy is ineffective [14,22].

Graph 2. On 5 different programs over a period of 24 or 48 weeks SVR registration frequency in 219 CHC patients receiving treatment



Number of patients	43 (23)	39 (21)	69 (47)	47 (27)	21 (21)

(In parentheses: Number of CHC patients caused by genotype 1)

1 – UKR (3 mln IU) + RV
2 – UKR (6 mln IU) + RV
3 – PEG-IFN + RV
4 – PEG-IFN + ZD
5 - PEG-IFN + RV + DAAD

PATIENT EVALUATION OF TREATMENT AND SIDE EFFECTS.

In the prospective observation, we identified the main clinical and toxicological features of UKR used for the AT of 67 patients with CHB and 82 patients with CHC. These patients were prescribed UKR in a single dose of 3 million IU. Determining the spectrum and manifestations of UKR side effects, we retrospectively compared them with similar results obtained during the observation of 120 hepatitis B patients who had previously received 3 million doses of roferon A.

The incidence of most "early" manifestations of Ukraferon side effects was slightly different from the incidence of similar manifestations in patients receiving roferon A.

We compared the recording frequencies of these manifestations of Ukraferon and roferon A side effects, and this difference was by no means statistically consistent. The "early" manifestations of the side effects of both IFNs were satisfactory by the patients, and although their moderate manifestations had individual changes, they did not require any drug correction. In addition, the frequency of these "early" manifestations in patients with CHB differed little from that of patients with CHC [4,20].

Then, the spectrum and frequency of "delayed" side effects that occurred during 6 weeks of use of the drug and were the main reason for the patient's refusal or incomplete treatment were determined.

At the end of the third month of treatment, the typical "delayed" side effects for both drugs were leukopenia and thrombocytopenia. Other side effects of IFN drugs were less common. At the same time, the incidence of these symptoms in patients receiving ukraferon did not differ practically from the same indicators in patients receiving roferon A, and the difference between these indicators was not statistically significant.

The "delayed" manifestations of side effects in patients receiving both IFNs did not go beyond the list of side effects reported by the manufacturers of the relevant IFN drugs. All "delayed" manifestations of side effects of both IFNs were less noticeable, and the drugs were administered satisfactorily by patients. This allowed us to confirm that the spectrum and expression of the "delayed" manifestations of ukraferon side effects did not differ from roferon A in practice. This meant that the reactogenicity of ukraferon and roferon A could be considered equal due to the risk of developing "delayed" side effects [6,20].

Evaluating the side effects of pegasys, we analyzed the results of observations of 56 CHB (receiving pegasis in monotherapy) and 69 CHC patients (receiving treatment under pegasys + RV). We compared the results with published data from 180 patients with chronic hepatitis (control group) who had previously received the same treatment. It was found that none of the indicators of side effects mentioned in the observation group, such as “early” or “delayed”, had a statistically constant difference ($p < 0.05$) from the corresponding indicators in the control group. This allowed us to consider the results of our clinical and toxicological observations to determine the manifestations of the side effects of pegasis [29].

Finally, let us note the results of clinical and neurological examination of 45 CHC patients injected with pegasis in standard doses and regimens. None of them has a history of psychoneurological or mental disorders. Examinations were performed before and 3 months after the start of treatment. In this study, these patients were diagnosed with the “neuropsychic” toxicity of IFN. Psychoemotional status was assessed by the survey, and the condition of the central and peripheral nervous system was assessed using a set of traditional clinical methods. We compared the frequency of these similar isymptoms published observations in 42 CHC patients previously treated with roferon A. We recorded this group of patients as a control group. Signs of neuropsychic toxicity were observed in 62.2% of patients injected with PEG-IFN during the observation period. In the control group, this indicator was

73.8%, there was no difference between them in the range $p < 0.05$. This showed that PEG-IFN drugs do not differ in principle from pharmaco-toxicological drugs r-IFN [13].

Given that the state of the immune system can play an important role in the therapeutic effect of antiviral therapy, we, together with the staff of the Immunology Laboratory of the Scientific Research Institute of Hematology and Transfusiology named after B. Eyvazov, CD3 (T-lymphocytes), CD4 (T-helper lymphocytes), CD8 (T-suppressor lymphocytes), CD19 (B-lymphocytes) and CD16 / 56 (NK-lymphocytes). Were also studied to determine the nature of the effect on blood composition. Using a laser needle cytometer, we immunologically examined the blood samples of 55 CHC patients twice - before treatment and 1 month after its start. 20 of these patients received treatment under the "r-IFN + RV" program, 20 under the "PEG-IFN + RV" program and 15 under the "PEG-IFN + RV + DAAD" program. It was found that the manifestations of changes in immunograms were higher in patients receiving antiviral therapy under the program, which included r-IFN drugs. PEG-IFNs had a less pronounced immunotropic effect [30].

RESULTS

1. Currently, treatment for chronic hepatitis B and C can be carried out not only with the use of traditional human interferons (IFNs), but also with many other antiviral drugs [5,8,11].
2. Although it can be used in the treatment of patients with CHB with both IFN drugs and nucleoside analogues, IFN drugs retain their importance as first-line drugs [7,25].
3. Consecutive application of antiviral drugs based on IFN drugs and nucleoside analogues allows increasing the final effectiveness of antiviral therapy [16,17].
4. At present, the treatment of CHC patients is based on the combined use of several antiviral drugs, among them IFN drugs in combination with ribavirin can be used effectively in the treatment of CHC patients caused by a virus that does not belong to genotype 1 [9,13,14].

5. r-IFN drugs partially lag behind PEG-IFN drugs in terms of therapeutic efficacy and do not differ significantly from these drugs in terms of spectrum and manifestations of side effects [4,6,12,18].

6. Recombinant IFN drugs can be used instead of the prescribed IFN drugs in the treatment of patients with CHB and CHC with limited funding for treatment [19,20,22].

PRACTICAL RECOMMENDATIONS

1. Antiviral therapy of patients with primary CHB who need treatment and do not have appropriate contraindications should begin with the appointment of PEG-IFN or r-IFN drugs.

2. In cases where treatment with IFN drugs is ineffective and poorly performed, treatment of patients with CHB may be continued with antiviral drugs from the group of nucleoside analogues.

3. In case of contraindications to the use of IFN drugs, treatment of patients with CHB should begin with the appointment of antiviral drugs from the group of nucleoside analogues.

4. Currently, the most effective treatment for patients with CHC is a combination of drugs from the group of enzymes of viral inhibitors. However, treatment of CHC patients who need treatment in limited circumstances and do not have appropriate contraindications can be carried out in combination with RV with the appointment of PEG-IFN or r-IFN in limited circumstances.

5. In cases where the combined initial therapy of IFN drugs with RV is ineffective or poorly conducted, further treatment of patients with CHC should be carried out with antiviral drugs from the group of enzymes of viral inhibitors.

6. Treatment of patients with contraindications to IFN or with low chances of successful treatment with the IFN + RV program (CHC caused by genotype 1 virus) should begin with the administration of drugs from the group of viral enzyme inhibitors.

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Conditional abbreviation

AT – antiviral therapy
BOC – boceprevir
CHB – Chronic Hepatitis B
CHC − Chronic Hepatitis C
DAAD – direct-acting antiviral drugs
DNA – deoxyribonucleic acid
ENT – entecavir
İFN – human interferon
IU – international unit
LAM – lamivudin
PCR – Polymerase chain reaction
PEG-İFN – pegylated interferon
RV – ribavirin
RNA − ribonucleic acid
r-İFN − recombinant alfa-interferon
SOF – sofosbuvir
SVR – sustained virological response
TEL – telbivudin
TVR – telaprevir
UKR – ukraferon

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