EFFECTIVENESS AND SAFETY OF TREATMENT WITH DOMESTIC CEPEGINTERFERON ALPHA-2B IN PATIENTS WITH CHRONIC HEPATITIS C INFECTION. ACTUAL CLINICAL EXPERIENCE

Tkacheva SV[1] ✉, Manapova ER[1], Sozinova YuM[1,2], Yakupova FM[1,2], Fazylova YuV[3]

[1] Department of Infectious Diseases, Faculty of Medical and Preventive Care, Kazan State Medical University, Kazan, Russia

[2] Diagnostic and Consultation Unit, Agafonov Republican Clinical Hospital of Infectious Diseases, Kazan, Russia

[3] Department of Dental Therapy, Faculty of Dentistry, Kazan State Medical University, Kazan, Russia

Interferon-based regimens for chronic hepatitis C (HCV) are quite common, just like interferon-free treatments, and are extensively used in Russia because interferon is widely available to most patients. In 2013 the original Russian drug cepeginterferon alpha-2b (cepegIFN alpha-2b marketed as Algeron by Biocad, Russia) was introduced into clinical practice. The aim of this study was to assess effectiveness and safety of cepegIFN alpha-2b as part of the combination therapy with ribavirin in patients with chronic HCV infection. The study was conducted over the period from 2014 to 2016 and recruited 37 patients with chronic genotype 1 HCV infection: 22 men and 15 women (mean age of 42.0 ± 5.2 years). All of them received the following combination antiviral therapy (AT): 1.5 μg/kg cepegIFN alpha-2b once a week and 15 μg/kg ribavirin daily over the period of 48 weeks. Effectiveness of AT was assessed by the rate of sustained virological response (SVR), i. e. aviremia achieved 24 weeks after the onset of treatment. In our SVR was observed in 26 patients (70.3 %). Adverse effects seen in the course of AT were typical of interferon-based drugs and ribavirin. CepegIFN alpha-2b dosage was corrected in two patients who developed neutropenia; ribavirin dosage was corrected in 3 patients who developed anemia. Based on the obtained results, we recommend including cepegIFN alpha-2b into the combination antiviral therapy in patients with chronic HCV infection.

Keywords: chronic hepatitis C, HCV infection, antiviral therapy, cepeginterferon alpha-2b, ribavirin, virological response, treatment effectiveness

✉ **Correspondence should be addressed:** Svetlana Tkacheva
ul. Butlerova, d. 49, Kazan, Russia, 420012; tkacheva-kgmu@mail.ru

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ЭФФЕКТИВНОСТЬ И БЕЗОПАСНОСТЬ ПРИМЕНЕНИЯ ОТЕЧЕСТВЕННОГО ЦЕПЭГИНТЕРФЕРОНА АЛЬФА-2В В ТЕРАПИИ ХРОНИЧЕСКОГО ГЕПАТИТА С. ОПЫТ РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКИ

С. В. Ткачева[1] ✉, Э. Р. Манапова[1], Ю. М. Созинова[1,2], Ф. М. Якупова[1,2], Ю.В. Фазылова[3]

[1] Кафедра инфекционных болезней, медико-профилактический факультет, Казанский государственный медицинский университет, Казань

[2] Консультативно-диагностическое отделение, Республиканская клиническая инфекционная больница имени А. Ф. Агафонова, Казань

[3] Кафедра терапевтической стоматологии, стоматологический факультет, Казанский государственный медицинский университет, Казань

В настоящее время для лечения хронического гепатита С (ХГС) используют как безинтерфероновые, так и интерферонсодержащие схемы противовирусной терапии. Последние достаточно широко используются в России за счет доступности препаратов интерферона широким слоям населения. С 2013 г. в клинической практике используется оригинальный российский препарат — цепэгинтерферон альфа-2b (цепэгИФН альфа-2b; торговая марка «Альгерон», «Биокад», Россия). Целью настоящего исследования являлась оценка эффективности и безопасности цепэгИФН альфа-2b при его применении с рибавирином для лечения пациентов с ХГС. Исследование было проведено в 2014–2016 гг., в нем приняли участие 37 пациентов с ХГС (генотип вируса 1): 22 мужчины и 15 женщин (средний возраст — 42,0 ± 5,2 года). Все они впервые получали комбинированную противовирусную терапию (ПВТ): цепэгИФН альфа-2b в дозе 1,5 мкг/кг/нед. и рибавирин в дозе 15 мг/кг/сут. в течение 48 недель. Эффективность ПВТ оценивали по частоте достижения устойчивого вирусологического ответа (УВО) — авиремии через 24 недели после ПВТ. В нашем исследовании УВО достигли 26 пациентов (70,3 %). Зарегистрированные на фоне ПВТ нежелательные явления были характерными для интерферона и рибавирина. Дозу цепэгИФН альфа-2b в связи с развитием нейтропении корректировали 2 пациентам, дозу рибавирина в связи с развитием анемии — 3 пациентам. Полученные результаты позволяют рекомендовать цепэгИФН альфа-2b для включения в схемы комбинированной противовирусной терапии для лечения больных с ХГС.

Ключевые слова: хронический гепатит С, вирус гепатита С, противовирусная терапия, цепэгинтерферон альфа-2b, рибавирин, вирусологический ответ, эффективность лечения

✉ **Для корреспонденции:** Ткачева Светлана Васильевна
ул. Бутлерова, д. 49, г. Казань, 420012; tkacheva-kgmu@mail.ru

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Currently, 2 to 3 % of the world population are infected with hepatitis C [1, 2]. It is known that HCV infection can progress asymptomatically. Without treatment some patients develop liver fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma [1–3].

Antivirals are a standard treatment for chronic hepatitis C (CHC). According to European and Russian clinical guidelines, antiviral therapy (AVT) should be prescribed to all HCV-infected patients; however, there are patients who require immediate AVT and those whose AVT can be delayed [1, 2].

There are interferon-based and interferon-free regimens for AVT. First-line therapy is based on the use of pegylated interferon alpha (PEG-IFN) in combination with ribavirin [1–3]. PEG-IFN is obtained by attaching an interferon molecule to a polymer called polyethylene glycol. The therapeutic effect of PEG-IFN is determined by interferon that exhibits antiviral, immunomodulatory and antiproliferative properties. Conjugation with polyethylene glycol increases the molecular weight of the resulting molecule, which prolongs IFN-alpha circulation in the blood.

Cepeginterferon alpha-2b, an original drug marketed as Algeron (Biocad, Russia), is one of the relatively inexpensive PEG-IFNs available on the Russian market, with polyethylene glycol molecular weight of 20kDa. It has been used in the clinical routine since 2013 [4, 5]. Unlike other interferon-based drugs, such as PEG-IFN alpha-2a or PEG-IFN alpha-2b, cepeginterferon alpha-2b has a single isomer, which makes its composition homogenious and ensures stable antiviral activity. So far, clinical trials have shown its sufficient effectiveness and an acceptable safety profile in comparison with other PEG-IFNs, and the drug was subsequently included into double and triple antiviral therapy regimens [6, 7]. It should be noted that AVT regimens based on cepegIFN-alpha 2b are available to the majority of HCV-infected Russian, due in no small part to its relatively low cost. In this light, its effectiveness, safety and tolerance should be widely discussed [5, 7].

The aim of this study was to assess effectiveness and safety of combination therapy with cepegIFN alpha-2b and ribavirin in patients with chronic HCV infection in the clinical setting.

METHODS

The study was conducted at the facilities of Agafonov Republican Clinical Hospital of Infectious Diseases, Kazan, in 2014–2016. The study enrolled 37 patients with CHC: 22 men and 15 women aged 23 to 65 years (mean age was 42.0 ± 5.2 years). Forty-five percent of patients had been infected for up to 5 years by the time of the study. All participants received a previously untried combination AVT with 1.5 μg/kg cepegIFN alpha-2b per week and 15 μg/kg ribavirin per day for 48 weeks.

In preparation for the treatment , at weeks 4, 12, 24 and 48 of the treatment, and 24 weeks after the treatment, a number of tests were carried out, including (1) the enzyme linked immunosorbent assay (ELISA) to detect the presence of anti-HCV and anti-HBsAg antibodies using the Multiskan Ascent plate reader (Agiletn Technologies, USA) and the Best reagent kit by Vector-Best, Russia; (2) determination of the viral load and genotyping of viral RNA using real-time polymerase chain reaction (sensitivity of 15 mU/ml); a viral load of $> 8 \times 10^5$ mU/ml viral RNA copies was considered high; these tests were run using the Rotor Gene-Q real-time PCR cycler (Qiagen, Germany); (3) the analysis of *IL28B* single nucleotide polymorphisms *rs8099917* and *rs12979860* (reagents used: the AmpliSense reagent kit by Interlabservice, Russia); (4) ultrasound imaging of the hepatobiliary system; (5) transient elastography of the liver with FibroScan 502 Touch (Echosens, France); (6) liver function tests, protein profile, full blood count, urinalysis; (7) ultrasound imaging of the thyroid and measuring the levels of the thyroid stimulating hormone, triiodothyronine (T3), thyroxine (T4), and thyroid peroxidase antibodies; (8) determination of ANA, AMA, ASMA, and LKM antibodies in the blood, if clinically indicated; (9) the examination of the periodontium followed by treatment, if necessary.

To assess treatment safety, we recorded every change in patients' general condition and deviations from the norm detected by blood tests. Side effects were evaluated using the CTCAE (Common Terminology Criteria for Adverse Events) [6].

Treatment effectiveness was assessed based on the frequency of sustained virologic response (SVR), or aviremia, 24 weeks after the treatment was complete.

Statistical analysis was performed using MS Excel-2007 and the Student's t-test.

The study was approved by the Ethics Committee of Agafonov Republican Clinical Hospital of Infectious Diseases (Protocol No. 4 dated December 17, 2013). All patients gave their informed consent.

RESULTS

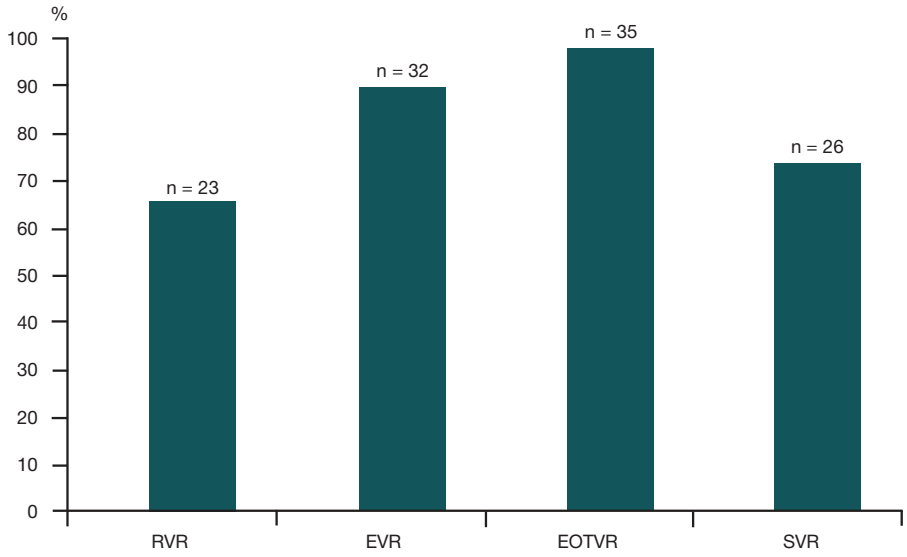
Genotyping revealed that all patients were infected with genotype 1 HCV (subtype 1b was identified in 36 patients; one patient was infected with subtype 1a). The viral load was low in 56.8 % of patients (n = 21). The samples of 84 % (n = 31) of patients were screened for *IL28B* polymorphisms to reveal that 58 % of them had favorable *IL28B* genotypes: CC (*rs12979860*) and TT (*rs8099917*).

Fibroscans detected no signs of fibrosis (F0 METAVIR) in 48.6 % of patients; mild and moderate fibrosis (F1–F2 METAVIR) was observed in 17.1 % and 14.3 % of patients, respectively. Marked fibrosis (F3–F4) was detected in 20 % of patients. There were no patients with cirrhosis.

The patients were distributed into groups based on the type of the virologic response achieved at different stages of AVT and at week 24 of posttreatment follow-up, as shown in the figure below. Rapid virologic response (RVR) at week 4 of the treatment was observed in 62.2 % of patients; early virologic response (EVR) at week 12 of the treatment was observed in 86.5 % of patients; end-of-treatment virologic response (EOTVR) was observed in 94.6% of the participants. Sustained virologic response was achieved in 26 patients (70.3 %).

Before the treatment, the majority of patients had elevated levels of alanine aminotranspherase (ALT), the average ALT level being 76.22 ± 4.77 U/l. In the course of treatment, the ALT dynamics was positive: at weeks 4 and 12 of treatment, ALT levels were down to 38.2 ± 3.11 U/l ($p < 0.05$) and 31.37 ± 1.27 U/l ($p < 0.05$), respectively. By the end of treatment, ALT was within a range of reference values in 92 % of patients (n = 34).

Treatment safety was assessed based on changes in patients' general health and deviations from the norm detected by blood tests. The observed adverse effects were typical of interferon and ribavirin: flu-like and asthenic-vegetative syndromes (weakness, poor performance at work, fatigue), and were observed in 36 patients. The flu-like syndrome occurred in the beginning of treatment and was eliminated by the intake of nonsteroidal antiinflammatory drugs. Skin reactions, such as dryness, itching, or rashes, were seen in 66.7 %. Increased



RVR — rapid virologic response at week 4 of treatment
EOTVR — end-of-treatment response at week 48 of treatment
EVR — early virologic response at week 12 of treatment
SVR — sustained virologic response at week 24 of posttreatment follow-up

Distribution of patients into groups based on the type of virologic response. Each patient can be included into more than one group depending on his/her response to therapy

irritability and mood changes were observed in 61.2 % of patients.

Blood tests indicated neutropenia, anemia and thrombocytopenia (see the Table). Grades 1 and 2 anemia (according to the CTCAE scale) was observed in 89.2 % patients. One patient was prescribed leucostim (300 μg, taken twice over the period of two weeks with a 7-day interval) at week 4 of the treatment because of neutropenia (neutrophil count went back to normal after leucostim therapy). Grades 1 and 2 thrombocytopenia was detected in 35.1 % of patients.

The dose of cepegIFN alpha-2b was corrected in 2 patients who developed neutropenia; ribavirin dose was corrected in 3 patients who developed anemia.

DISCUSSION

The obtained results demonstrate high effectiveness (70.3 % of patients with sustained virologic response) and safety of a combination AVT with cepegIFN alpha-2b in patients with chronic HCV. Our data are consistent with the results of other studies [6–11]. For example, in a randomized comparative clinical study aimed to assess effectiveness and safety of 1.5 μg/kg and 2.0 μg/kg doses of cepegIFN alpha-2b taken in combination with ribavirin [6], sustained virologic response was achieved in 71.4 % of patients (cepegIFN alpha-2b dose of 1.5 μg/kg). In another study [7], SVR was achieved in 64.6 % of patients with genotype 1 HCV, while in patients with positive predictors of treatment outcome, this proportion was 75.0 %.

No serious adverse events were observed in any of the participants; all side effects were expected and typical of pegIFN alpha and ribavirin. Therefore, a combination therapy with cepegIFN alpha-2b and ribavirin is a reasonable choice for patients with predictors of positive response to AVT (mild fibrosis, low viral load, favorable *IL28B* polymorphisms, no comorbidities).

CONCLUSIONS

Sustained virologic response to a combination therapy with a cepegIFN alpha-2b and ribavirin was achieved in 70.3 % of patients with chronic HCV infection. All adverse effects were not unexpected and did not require termination of treatment. Considering that interferon-free regimens for antiviral therapy are unavailable to the majority of the Russian population, interferon-based treatment is a good choice for patients with genotype 1 HCV due to its relatively high effectiveness and safety.

Blood counts of patients with chronic HCV infection before, during and 24 weeks after the antiviral therapy. Data are represented as M ± m, n = 37

Parameters	Observation period					
	before treatment	week 4 of treatment	week 12 of treatment	week 24 of treatment	week 48 of treatment	24 weeks after treatment
WBC × 10^9 cells/L	5.5 ± 0.16	3.4 ± 0.12**	3.3 ± 0.11**	2.7 ± 0.16***	2.8 ± 0.18***	4.2 ± 0.26
RBC × 10^{12} cells/L	4.7 ± 0.06	4.0 ± 0.08	3.6 ± 0.06*	3.4 ± 0.09*	3.5 ± 0.08*	4.4 ± 0.06
HGB, g/L	141.5 ± 2.0	116.0 ± 3.0*	113.0 ± 2.9*	111.0 ± 2.8**	112.0 ± 4.02**	137.0 ± 1.2
PLT × 10^9 cells/L	220.0 ± 8.2	161.1 ± 8.4*	157.0 ± 9.1***	171.5 ± 8.0*	151.0 ± 9.96**	224.0 ± 8.1

Note. * — $p < 0.05$, ** — $p < 0.01$, *** — $p < 0.001$ when comparing blood counts before and during the treatment.

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