AN ANALYSIS COMPARING THE EFFICACY OF NARLAPREVIR WHEN COMBINED WITH INTERFERON AND INTERFERON-FREE THERAPY REGIMENS FOR INDIVIDUALS SUFFERING FROM CHRONIC HEPATITIS C

Raupov Abdurahmon Ortiq o'gli,
Bukhara Innovative Education and Medical University.
Bukhara .Uzbekistan.

Sharipova Nigina Qudrat qizi
Bukhara State Medical Institute.
Bukhara .Uzbekistan.
rao.biti.22@gmail.com

Annotation: This article presents a comparative analysis of the efficacy of narlaprevir in conjunction with two different treatment regimens, namely interferon-based therapy and interferon-free therapy, in individuals with chronic hepatitis C. The authors investigate various clinical parameters such as virological response rates, treatment duration, adverse effects, and sustained virologic response (SVR) rates to assess the effectiveness of narlaprevir within each treatment protocol. By examining both traditional interferon-based therapy and newer interferon-free regimens, the study offers insights into the evolving landscape of hepatitis C treatment options. The findings contribute to the understanding of optimal treatment strategies for chronic hepatitis C patients, with implications for clinical decision-making and healthcare policy development. This analysis aims to inform healthcare practitioners and policymakers about the relative efficacy and safety profiles of narlaprevir in different treatment contexts, ultimately aiming to improve patient outcomes in the management of chronic hepatitis C.

Keywords: chronic hepatitis C, liver cirrhosis, antiviral therapy, daklatasvir, interferon, narlaprevir, ritonavir.

Introduction. Throughout the world, chronic hepatitis C (CHC) continues to be one of the most pressing health problems due to its high morbidity and the likelihood of adverse outcomes . Currently developed highly effective antiviral therapy (AVT) regimens using direct antiviral drugs (DAAs) allow achieving a sustained virological response (SVR) in the vast majority (90–95%) of cases. However, such optimistic sentiments are offset by the fact that access to DAAs produced abroad is limited due to their high cost . The first and so far the only Russian oral inhibitor of hepatitis C virus (HCV) NS3/4A-serine protease is narlaprevir. Its combination with the boosting agent ritonavir can significantly increase the rate of SVR registration in patients with HCV genotype 1b. In addition, the pharmacokinetic characteristics of this combination provide a convenient regimen for the patient - only 1 time per day. It is impossible not to note the pharmacoeconomic advantages of narlaprevir over other DAAs. Thus, when calculating the costs of conducting a full course of AVT using narlaprevir, the savings are 35–38%. Narlaprevir has a synergistic effect with pegylated interferon-α2a (Peg-IFN-α2a)/ribavirin (RBV) and daclatasvir, which has made it possible to successfully use it both as part of interferon-containing and interferon-free treatment regimens

The purpose of the study.

Our objective was to present a comparative assessment of the effectiveness of narlaprevir in conjunction with interferon-free mode and pegylated interferon-alpha-2a (Peg IFN-alpha-2a) in patients with chronic hepatitis C (CHC).

Materials and methods of research.

Study design and participants.

The prospective cohort study involved 187 patients: 156 people with CHC and 31 with liver cirrhosis (LC) class A according to the Child–Pugh classification. When developing the study design, we took into account modern recommendations for the treatment of patients with CHC.

Conditions.

The clinical base for the study was the Bukhara Multidisciplinary Hospital in 2022-2024.

Eligibility Criteria.

Inclusion criteria:

1) age ≥18 years;

2) detection of HCV genotype 1b RNA in the blood, regardless of the level of viremia and the stage of fibrosis;

3) absence of alcohol and drug addiction;

4) absence of mixed hepatitis (HCV+HBV), HIV infection, as well as severe concomitant diseases with a prognostically limited life expectancy.

Subgroup analysis.

In accordance with the objectives of the study, we formed 2 groups of patients. Group 1 (n=107) included patients who received narlaprevir at a dose of 200 mg once a day, ritonavir - 100 mg once a day, Peg-IFN-α2a - 180 mcg subcutaneously once a week and RBV at a dose depending on body weight (1000–1200 mg/day) for 12 weeks, after which standard "double" therapy (Peg-IFN-α2a + RBV) was continued until 24 weeks. Patients in group 2 (n=80) underwent AVT in an interferon-free regimen. They received narlaprevir 200 mg once daily, ritonavir 100 mg once daily, and daclatasvir 60 mg once daily for 12 weeks.

Methods for assessing target indicators.

The effectiveness of AVT was assessed by the rate of achieving SVR 24 weeks after completion of treatment. HCV RNA levels were determined using the TagMan HCV Quantitative Test v. 2.0" (Roche Diagnostics, Switzerland) with a threshold of analytical sensitivity of 15 IU/ml.

During the HTP, clinical and laboratory monitoring was carried out, including:

1) examination of the patient and clinical blood test once every 2 weeks;

2) biochemical blood test - total and conjugated bilirubin, alanine (ALT) and aspartate aminotransferase activity - once every 2 weeks;

3) assessment of the safety profile - monitoring the development of adverse reactions (AR), including testing patients on the Beck Depression Scale (for those receiving IFN-α drugs);

4) qualitative determination of the level of HCV RNA after the 4th and 12th weeks of treatment, and in patients receiving AVT using interferon-containing regimens - additionally after the 24th week of treatment.

Statistical analysis.

Statistical data processing was carried out using Statistica v. software. 10.0 for Windows XP (StatSoft Inc., USA). The work used descriptive statistics (arithmetic mean, standard error of the mean, median), Student's t-test. Differences were considered statistically significant at $p<0.05$.

The results of the study.

According to their initial characteristics (gender, age, specific body weight of patients with "advanced" stages of liver fibrosis FIII–IV, as well as the level of viral load), the groups were completely comparable (Table 1). From the table 1 it follows that in both groups the ratio of patients by gender was almost the same. People of working age predominated. The proportion of patients with cirrhosis in the compared groups did not have statistically significant differences and amounted to 14.9 and 18.8%, respectively ($p>0.05$). 6.2% of patients in group 1 and 8.8% of patients in group 2 had "unsuccessful" experience of the previous course of treatment ($p>0.05$).

Studies have shown that with AVT using narlaprevir in combination with Peg-IFN-α2a/RBV, a rapid decrease in viral load occurs. Thus, after 2 weeks from the start of therapy, HCV RNA was not detected in 74.8% of patients. Similar results were obtained in a group of patients receiving narlaprevir in combination with daclatasvir and ritonavir. By the specified period of treatment, aviremia was achieved in 83.8% of patients ($p>0.05$).

Table 1.

Initial characteristics of patients, included in the study

Indicators	Group 1 (n=107)	Group 2 (n=80)

Average age, years	47,6±1,2	44,1±1,3
Age range, years	18–71	19–76
Men/women, n (%)	58 (54,2)/49 (45,8)	38 (47,5)/42 (52,5)
ALT≥3 times higher than the normal limit, n (%)	10 (9,3)	8 (10,0)
Thrombocytes <150,0×109/l, *n* (%)	22 (20,6)	17 (20,0)
HCV RNA >500 thousand IU/ml, n (%)	43 (40,2)	37 (46,3)
Average viral load level, lg IU/ml	6,1±0,3	6,4±0,5
Genotype 1b, n (%)	107 (100)	80 (100)
Liver cirrhosis, n (%)	16 (14,9)	15 (18,8)
“Unsuccessful” previous HTP experience, n (%)	9 (6,2)	7 (8,8)

An early virological response was obtained in 105 (98.1%) patients treated with narlaprevir as part of an interferon-containing AVT regimen, and in 77 (96.3%) patients treated in an interferon-free regimen (p>0.05). The full course of AVT was completed by 101/107 (94.4%) patients who were prescribed narlaprevir in combination with PegIFN-α2a/RBV. During treatment, adverse events were recorded that were fully consistent with those that usually occur during standard “double” therapy for CHC using Peg-IFN-α2a/RBV. These include fever, weakness, RBV-induced thrombocyto- and neutropenia. The reasons for early termination of treatment in our study were RBV-induced anemia with a hemoglobin concentration of 76 g/l (n=1), febrile neutropenia (n=1), depressive states (n=2) and severe asthenic syndrome with categorical refusal to continue treatment (n=2;). Thus, the frequency of ADRs requiring discontinuation of AVT was 5.6%. At the same time, there were no cases of early treatment discontinuation among patients receiving AVT in an interferon-free regimen. However, when assessing the safety profile of the narlaprevir/daclatasvir regimen, we took into account any changes in health and abnormalities in laboratory parameters. It is noteworthy that in this group of patients ADRs occurred no earlier than the 4th week of treatment. Their severity was insignificant. Thus, 6 (7.5%) patients had moderate epigastric pain. Weakness was noted by 12 (15%) patients. At the same

time, none of the patients we observed showed negative dynamics in laboratory parameters.

Fig. 1

Dynamics of average ALT levels before treatment and at different times of antiviral therapy.

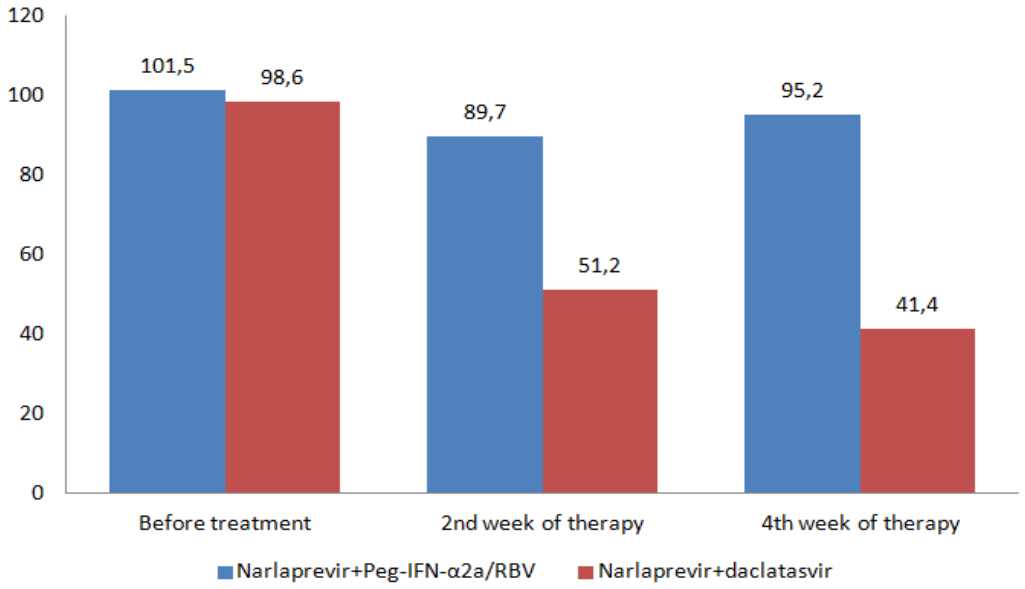
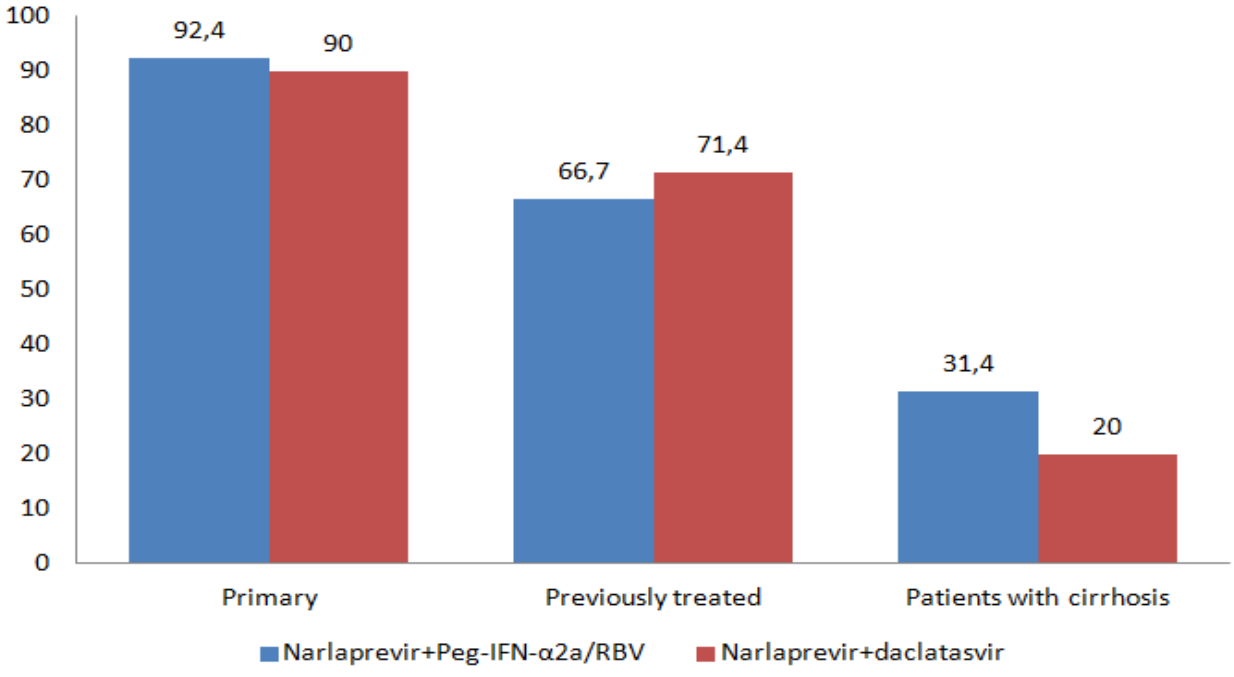


Fig. 2

The incidence of SVR24 in different patient categories.



When assessing the dynamics of ALT activity (Fig. 1), it was found that by the 12th week of treatment, the average value of this indicator in the group of patients receiving narlaprevir in combination with Peg-IFN-α2a and RBV was statistically significantly higher than when using narlaprevir with daclatasvir (92.5±7.6 and 41.4±5.8 U/l, respectively; $p<0.0001$).

However, in a comparative analysis of the SVR rate 24 weeks after completion of AVT (SVR24), we found that the effectiveness of the treatment regimens we studied was almost the same (Fig. 2). In our study, the SVR24 rate in the overall group of patients receiving narlaprevir in combination with Peg-IFN-α2a/RBV was 92.4%, and in the comparison group – 90% ($p>0.05$). When analyzing the SVR24 registration rate in previously treated patients, the following data were obtained: in patients receiving narlaprevir in combination with PegIFN-α2a, the SVR24 rate was 66.7%. When previous therapy was ineffective in another group of patients, this figure was equal to 71.4%, demonstrating the absence of significant differences between the compared groups ($p>0.05$). The rate of achieving SVR24 in patients with cirrhosis was subjected to a separate analysis. As studies have shown, in both groups of patients with cirrhosis it turned out to be quite low. Thus, in patients receiving narlaprevir in combination with Peg-IFN-α2a, it was 31.5%, and when using an interferon-free AVT regimen, it was only 20%.

Discussion

Currently, various interferon-containing and interferon-free AVT regimens have been proposed for patients with CHC . Scientific data have emerged on the high effectiveness of narlaprevir, the only Russian oral inhibitor of HCV NS3/4A serine protease. This drug can be used to treat patients with CHC caused by HCV genotype 1b in combination with both Peg-IFN-α2a/RBV and daclatasvir. The results obtained in our study indicate the high effectiveness of narlaprevir both in combination with Peg-IFN-α2a/RBV and with daclatasvir, but only in the early stages of the disease (FI-II on the METAVIR fibrosis scale). However, none of the studied treatment regimens has any advantages over the other in terms of

effectiveness. As for the prognosis of the effectiveness of narlaprevir, according to our data, the only predictor of “failure” of treatment is the presence of cirrhosis. It is also important to note that, in contrast to the combination of narlaprevir with PegIFN-α2a, the use of narlaprevir in an interferon-free regimen has a more favorable safety profile.

Conclusion

Real clinical practice indicates that the use of narlaprevir in an interferon-free regimen is not inferior in effectiveness to an interferon-containing treatment regimen and demonstrates a more favorable safety profile. With maximum efficiency, these treatment regimens can be equally used at the pre-cirrhotic stage of the disease (FI-II on the METAVIR fibrosis scale) and in patients who have not previously received AVT.

REFERENCES

1. Мазина Н.К., Мазин П.В. Современные подходы к решению проблем лечения вирусных гепатитов (обзор). Вятский медицинский вестник. 2017;3(55):73-8.

2. Рудакова А.В., Гусев Д.А., Усков А.Н., и др. Фармакоэкономические аспекты терапии ХГС (1 генотип) у пациентов, ранее не получавших противовирусные препараты. Журнал инфектологии. 2017;9(2):101-10

3. Nurbaev, F. E. (2022). Raupov AO Sharipova NK Dzhumaev H. Liver lesions in GOVID-19: etiology, clinic, prognosis, treatment and prevention. Bukhara scientific-abstract, spiritual and educational journal, 11, 49.

4. Бакулин И.Г. Нарлапревир – отечественный препарат прямого противовирусного действия для лечения хронического гепатита С. Результаты исследования PIONEER. Поликлиника. 2016;5(1):52-4.

5. Бурневич Э.З., Тихонова Ю.Н., Щаницина С.Е. Нарлапревир, бустированный ритонавиром, в комбинации с пегилированным интерфероном-α и рибавирином в лечении хронического гепатита С. Клиническая фармакология и терапия. 2014;23(5):34-9.

6. de Bruijne J, Bergmann JF, Reesink HW, et al. Antiviral activity of narlaprevir combined with ritonavir and pegylated interferon in chronic hepatitis C patients. Hepatology. 2010;52(5):1590-9. DOI:10.1002/hep.23899

7. Бурневич Э.З., Гусев Д.А., Знойко О.О., и др. Эффективность и безопасность нарлапревира/ритонавира в комбинации с даклатасвиром у ранее не получавших противовирусную терапию больных хроническим гепатитом С без цирроза печени, инфицированных вирусом гепатита С генотипа 1b. Клиническая фармакология и терапия. 2018;27(4):35-9.