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Предикторы спонтанного и посттерапевтического вирусного клиренса острого гепатита с: данные национального исследования

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Predictors of spontaneous and treatment-induced viral clearance of acute hepatitis c infection: the national research data

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Резюме

Введение. Наше исследование оценило предикторы спонтанного вирусного клиренса и вызванного лечением вирусного клиренса острого вирусного гепатита С.

Материалы и методы. В исследование были включены данные 286 пациентов (156 мужчин в возрасте 18–79 лет и 130 женщин в возрасте 18–81 года) с острым гепатитом С в Латвии за 5-летний период (с 2008-го по 2012 год). Мы провели ретроспективный анализ эпидемиологии, способа передачи, клинического течения, изменений лабораторных тестов (аланинаминотрансферазы, аспартатаминотрансферазы, общего билирубина, INR) и изменений УЗИ в попытке определить факторы, которые могли бы предсказать исход заболевания.

Результаты. Среди 286 исследованных пациентов выделены способы передачи вируса, связанные со здоровьем, которые были основным фактором риска у 45% пациентов, внутривенное употребление наркотиков у 11%, татуировка, пирсинг, маникюр — у 7%, передача половым путем — у 6%, травмы от укола иглой — у 3% и источник инфекции не определен у 28% пациентов. В нашем исследовании у 92% пациентов регистрировались жалобы, у 79% пациентов — желтуха. Гепатомегалия при УЗИ была отмечена в 13% случаев, а внутрибрюшная лимфаденопатия — в 38% случаев.

Спонтанный клиренс острого гепатита наблюдался у 41% пациентов. Мы не установили какой-либо значительной корреляции между спонтанным вирусным клиренсом и возрастом пациента, полом, клиническими особенностями или изменениями лабораторных тестов. Но мы наблюдали, что пациенты с интраабдоминальной лимфаденопатией при УЗИ выздоравливали чаще по сравнению с пациентами без интраабдоминальной лимфаденопатии (r=0,219, p=0,016).

Лечение интерфероном альфа 2b проводилось у 228 пациентов. 86% пациентов имели УВО после 6 месяцев после лечения, у 4% — рецидив. Мы обнаружили, что лечение интерфероном альфа 2b было более эффективным у женщин по сравнению с мужчинами (r=0,170, p=0,047). Мы не определили какой-либо существенной корреляции между эффективностью противовирусной терапии и клиническими особенностями и изменениями лабораторных тестов.

Заключение. Инфекция вируса гепатита С спонтанно проходит у 41% пациентов. Мы не можем предсказать самопроизвольный клиренс вируса опираясь на возраст, пол, клинические признаки или изменения лабораторных тестов, но пациенты с интраабдоминальной лимфаденопатией при УЗИ выздоравливали чаще по сравнению с пациентами без интраабдоминальной лимфаденопатии. Ни один из параметров не позволяет точно прогнозировать спонтанное разрешение на индивидуальном уровне.

Ключевые слова. Вирусный гепатит С, спонтанный клиренс

Summary

Background/Aims. Our study retrospectively evaluated the predictors of spontaneous viral clearance and treatment-induced viral clearance of acute viral hepatitis C.

Methods. The study included the data of 286 patients (156 male aged 18–79 years and 130 female aged 18–81 years) with acute hepatitis C in Latvia over a 5 year period (from 2008 till 2012). We performed retrospective analysis of the epidemiology, mode of transmission, clinical course, changes of laboratory tests (alanine aminotransferase, aspartate aminotransferase, total bilirubin, INR), changes of ultrasonography in an attempt to identify factors that could predict the outcome of the disease.

Results. Among the 286 patients studied, transmission associated with healthcare-related exposure was the primary risk factor in 45% of patients, intravenous drug use in 11%, tattooing, body piercing, manicures in 7%, sexual transmission in 6%, needle stick injuries in 3% and source of infection undetermined in 28% of patients. In our study 92% of patients noted complaints, 79% of patients presenting with jaundice. Hepatomegaly in ultrasound was reported in 13% of cases and intra-abdominal lymphadenopathy was reported in 38% of cases.

The spontaneous clearance of acute hepatitis was observed in 41% patients. We did not establish any significant correlation between spontaneous viral clearance and patient age, gender, clinical features or changes of laboratory tests. But we observed that patients with intra-abdominal lymphadenopathy in ultrasonography recovered more often compared to patients without intra-abdominal lymphadenopathy (r=0,219, p=0,016).

Treatment with interferon alpha 2b was generally initiated by 228 patients. 86% of patients had a SVR after a 6 months post-treatment follow-up, 4% relapsed. We found that treatment with interferon alpha 2b was more effective in women compared to men (r=0.170, p=0.047). We did not did not determine any significant correlation between efficacy of antiviral therapy and clinical features and changes of laboratory tests.

Conclusion. Hepatitis C virus (HCV) infection spontaneously clears in 41% of patients. We cannot predict spontaneous viral clearance by patient age, gender, clinical features or changes of laboratory tests, but patients with intra-abdominal lymphadenopathy in ultrasonography recovered more often compared to patients without intra-abdominal lymphadenopathy. None of the parameters accurately predicts spontaneous resolution at the individual level.

Keywords: Hepatitis C virus, spontaneous clearance

Introduction

Hepatitis C virus infection is one of the main causes of chronic liver disease worldwide. (1) Approximately 399 000 people die each year from hepatitis-C-related liver diseases. (2) Global prevalence of overall active hepatitis C infection with viremia estimated to be approximately 1%. (1) In Europe country-specific rates of all reported cases ranged from 0.3 cases per 100 000 population in Italy to 71.5 cases per 100 000 population in Latvia. (3)

Among various genotypes of hepatitis C virus, genotype 1 is the most prevalent which accounts for 46% of all hepatitis C virus infections, followed by genotype 3, which is 22% prevalent. Genotype 2 and 4 each has 13% prevalence. (1) Figure 1 illustrates global prevalence and genotype distribution. (4)

True incidence of new hepatitis C infection is difficult to determine because most cases are asymptomatic. (5) Latvia has one of the highest overall rates of reported hepatitis C in Europe. European surveillance data suggest the rate of reported acute cases in Europe of 0.3 per 100 000 population, ranging from <0.1 in Greece, Poland and the United Kingdom to 2.1 per 100 000 in Latvia in 2017. (3)

In 2016, the World Health Organization set a goal to eliminate viral hepatitis by 2030. (7)

In recent years, management of chronic hepatitis C virus infection has changed substantially because of the approval of highly curative, interferon-free direct-acting antiviral therapies. (8) (9) (10) Direct-acting

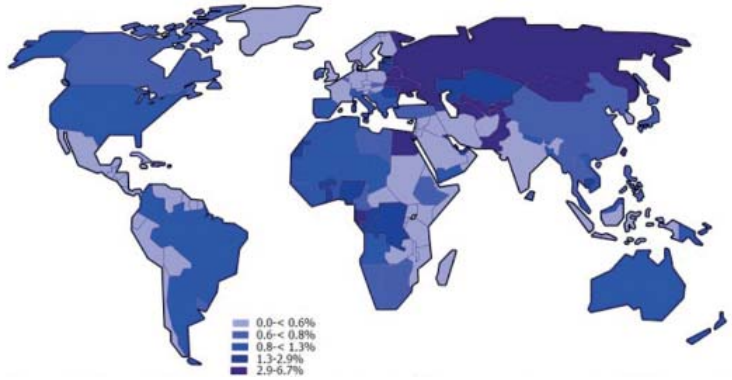

Рисунок 1.
Figure 1.

Source: Gower *et al*. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014 Nov; 61(1 Suppl): S45-57. DOI: 10.1016/j.jhep.2014.07.027. Epub 2014 Jul 30

Hepatitis C prevalence (percent of population)

antivirals (DAAs) against hepatitis C virus infection can achieve complete cure in >95% of cases. (11) (12)

Unfortunately regarding the treatment of acute hepatitis C, there are currently more questions than answers. There is no unitary guideline how to manage acute hepatitis C. A number of medical treatments have been used for acute infection, but the best way to treat it is not clearly established at the present moment.

Background/Aims

Our study evaluated the predictors of spontaneous viral clearance and treatment induced viral clearance of acute viral hepatitis C.

Materials and Methods

The study included the data of 286 patients (156 male aged 18–79 years and 130 female aged 18–81 years) with acute hepatitis C in Latvia over the 5 year period (from 2008 till 2012). We performed a retrospective analysis of the epidemiology, mode of transmission, clinical course, changes of laboratory tests (alanine aminotransferase, aspartate aminotransferase, total bilirubin, INR), changes of ultrasonography. We tried to find statistically significant correlation between these factors and outcome of the disease. The diagnosis was based on the presence of HCV RNA or seroconversion anti-HCV and clinical and biochemical criteria and the absence of a history of chronic liver disease or other causes of acute hepatitis. Patients were excluded if they had HIV infection. Due to limited financial resources, the latest, highly efficacious DAAs treatment was not available to everyone in the health care system in Latvia in that timeframe. In our study patients received 6 million U of interferon alfa-2b subcutaneously daily for the first 4 weeks and then three times per week for another 20 weeks. All patients were evaluated before, during and after treatment. Sustained virological response (SVR) was defined by undetectable HCV-RNA (using commercial qualitative polymerase chain reaction (PCR) methods) 6 months after the end of treatment. Patients with negative HCV-RNA at the end of treatment and positive 6 months later were considered relapse and patients with positive HCV-RNA at the end of treatment were considered non-responders. Spontaneous clearance without treatment was defined if the absence of HCV RNA was established six months after the initial test. The serial liver function tests, including aspartate aminotransferase, alanine aminotransferase and bilirubin were performed using standard assays.

Statistical analysis

Data analysis was performed using Microsoft Office Excel and SPSS version 17.0. Pearson's correlation coefficient and Spearman's rank correlation coefficient were used for correlation analyses. *P*-values lower than 0.05 were considered to indicate a statistically significant difference.

Results

Among the 286 patients studied, transmission associated with healthcare-related exposure was the primary risk factor in 45% of patients, intravenous drug use in 11%, tattooing, body piercing, manicures in 7%, sexual transmission in 6%, needle stick injuries in 3%, while the source of infection was undetermined in 28% of patients.

Symptomatic acute hepatitis C virus infection usually impacts only about 25%–30% of patients. (6) In our study 92% of patients noted complaints. The usual symptoms were nausea, anorexia, right upper abdominal discomfort, fatigue, flu-like symptoms and 79% of patients presenting with jaundice. Hepatomegaly in ultrasound was reported in 13% of cases and

intra-abdominal lymphadenopathy was reported in 38% of cases. This is likely to indicate that these diagnosed cases represent only a fraction of the number of acute hepatitis C patients and that a large proportion of patients who are asymptomatic are not diagnosed.

8% of patients were anti-HCV negative at initial clinical presentation, among these patients, 6 patients showed anti-HCV seroconversion.

Laboratory testing showed median ALT levels of 1467 IU/L (range: 64–7000), median aspartate aminotransferase level 1005 IU/L (range: 97–4786), median total bilirubin 130 mkM/L (range: 18,5–505).

The natural (untreated) course of acute hepatitis C, spontaneous clearance was observed in 41% patients. We did not establish any significant correlation between spontaneous viral clearance and patient age, gender, clinical features or changes of laboratory tests. But we observed that patients with intra-abdominal lymphadenopathy in ultrasonography recovered more often compared to patients without intra-abdominal lymphadenopathy (r=0,219, p=0,016).

Treatment with interferon alpha 2b was generally initiated by 228 patients. Only 56% patients received a full course of treatment, 20% did not initiate therapy and 24% patients discontinued therapy, most of them — in 83% arbitrarily for no unknown reason, in 3% patients noted that treatment could not be continued due to lack of money, one patient became pregnant and 12% patients could not continue treatment due to medication-related adverse reactions. Patients complained of fatigue, elevated temperature, headache, pain in the eyeballs, insomnia, drowsiness, dizziness, visual changes, depression, nervousness, weight loss, dyspepsia, hair loss, itchy skin and rash. 61% of treated patients developed thrombocytopenia, 61% leukopenia, 56% neutropenia, and 16% had changed TSH (decreased in 13% patients and 3% above normal). The average time from disease onset until the start of therapy was 25 days. 86% of patients had a SVR after a 6 months post-treatment follow-up, 4% relapsed. We found that treatment with interferon alpha 2b was more effective in women compared to men (r=0.170, p=0.047). We didn't find any significant correlation between efficacy of antiviral therapy and clinical features and changes of laboratory tests.

Discussion

Should we treat acute hepatitis C? Which patients should be treated?

Hepatitis C virus infection spontaneously clears in 20% to 50% of patients (6) As well in our study spontaneous clearance was observed in 41% patients. Predictors of spontaneous clearance include jaundice, elevated ALT level, hepatitis B virus surface antigen positivity, female sex, younger age, genotype 1 infection, and host genetic polymorphisms, most notably those near the IL28B gene and HLA class II. (6) (13) (14) (15), but none of these parameters accurately predicts spontaneous resolution at the individual level. (16) In our study we did not detect any significant correlation between spontaneous viral clearance and patient age, gender, clinical features or changes of laboratory tests.

According to AASLD-IDSA recommendations patients diagnosed with acute hepatitis C virus infection should initially be monitored with hepatic panels at 2- to 4-week intervals. (17) Laboratory monitoring should continue until the ALT level normalizes and HCV RNA becomes repeatedly undetectable, suggesting spontaneous resolution. If this does not occur, frequency of laboratory monitoring for patients with persistently detectable HCV RNA and elevated ALT levels should follow recommendations for monitoring patients with chronic HCV infection. Thus, detectable HCV RNA at 6 months after the time of infection will identify most persons who need antiviral therapy. (18)

European Association for the Study of the Liver recommends that patients with acute hepatitis C should be considered for antiviral therapy in order to prevent progression to chronic hepatitis C. Indeed, immediate treatment of acute hepatitis C with DAAs improves clinical outcomes and was shown to be highly cost-effective compared with deferring treatment until the chronic phase of infection. (16) (19)

What treatment regimen should be used?

The first pharmacological regimen for hepatitis C was introduced in the 1990s and consisted of non-pegylated interferon (IFN) alpha-2a or alpha-2b mono-therapy. (20) Cure rates of acute infection with IFN -based treatment are high. (21) A meta-analysis of 22 studies (n=1,075) using either standard interferon or peginterferon monotherapy reported an overall SVR rate of 78%. (22) In our study treatment with 6 million U of interferon alfa-2b achieved SVR in 86% of patients, 4% relapsed.

While interferon-based therapy has good efficacy in acute infection, the side effect profile limits implementation. Also in our study 12 % of patients could not continue treatment due to medication-related adverse reactions.

The treatment with DAAs is more effective and safe.

Three trials showed high SVR with the fixed-dose combination of sofosbuvir and ledipasvir in acute hepatitis C patients infected with genotype 1. (23) (24) (25)

The combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir yielded a 97% SVR rate in patients with acute or recent hepatitis C in the TARGET-3D study. (26)

Another two studies showed that the combination of sofosbuvir and ribavirin for either 6 or 12 weeks was not sufficient to achieve high SVR rates in patients with acute or early chronic hepatitis C. Sofosbuvir-ribavirin for 12 weeks for the treatment of acute HCV genotype-1 infection in HIV-1–infected person's resulted in a high relapse rate. (27) (28)

Dutch multicenter study observed that 8 weeks course of grazoprevir plus elbasvir was highly effective for the treatment of acute HCV genotype 1 or 4 infection. 99% of patients achieved SVR12. All patients who were infected with a virus carrying a clinically significant polymorphism in NS5A were cured. No adverse events led to study drug discontinuation. (29)

According to EASL recommendations patients with acute hepatitis C should be treated with a combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 and 6) or a combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1b). Based on similarities to chronic hepatitis C, patients with acute hepatitis C may be treated with a combination of sofosbuvir and velpatasvir (all genotypes), a combination of glecaprevir and pibrentasvir (all genotypes), or a combination of grazoprevir and elbasvir (genotypes1b and 4). (16)

According to AASLD-IDSA recommendations owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection. (18)

As mentioned above the present guidelines recommend interferon-free direct-acting antiviral treatment for acute HCV infection, because DAA are highly efficacious and more tolerable than interferon-based therapy, but still in many countries, patients are treating with IFN-based regimens, because DAAs are expensive (30) and because of the lack of insurance coverage of new DAAs.

When to start therapy? Whether therapy should be started immediately after diagnosis or delayed?

The ideal time point for starting acute hepatitis C virus infection therapy has not been firmly established. The results of studies are controversial.

An international collaboration of nine prospective cohorts studied 632 patients and found that the median time to clearance was 16.5 weeks with 34%, 67%, and 83% demonstrating clearance at 3, 6, and 12 months. (21) These results have led to recommendations to generally wait 6 months for the possibility of spontaneous clearance if a delay in treatment is reasonable.

In Italy randomized multicenter study observed that 130 mono-infected patients who were treated after a 12-week delay showed similar SVR rates as those in studies using a 4-week observation period (31).

In contrast, data from the German HepNET III study on acute hepatitis C virus mono-infection did not support a 12-week delay in treatment after diagnosis, as this was associated with a lower SVR rate than immediate treatment (SVR, 54% vs. 67%) (32)

As well previous meta-analysis of treatment with interferon based regimens of acute hepatitis C reported SVR24 rates of 82% if started within 12 weeks of diagnosis compared with SVR rates of 67% in those starting treatment between 12 weeks and 24 weeks and 62% in those starting treatment after 24 weeks. This study had demonstrated higher response rates for acute infection compared with chronic infection. (33)

In January 2019 published study showed results of mathematical model to the Dutch hepatitis C virus epidemic among HIV-infected MSM to compare three different DAA treatment scenarios: 1) immediate treatment, 2) treatment delayed to chronic infection allowing spontaneous clearance to occur, 3) treatment delayed until F2 fibrosis stage. This study shows that DAA treatment for acute hepatitis C is a cost-saving prevention approach that strongly reduces the hepatitis C virus epidemic among HIV-infected MSM. (34)

According current guidelines, if the clinician and patient decide that a delay in treatment initiation is acceptable, AASLD/IDSA recommend monitoring for spontaneous clearance for a minimum of 6 months. (18)

If a decision is made to initiate treatment during the acute infection period, AASLD/IDSA recommend monitoring HCV RNA for at least 12 to 16 weeks before starting treatment to allow for spontaneous resolution before treatment. (18)

Clinical situations which may favor early treatment over waiting for spontaneous clearance include:

- an increased risk for transmitting infection such as a surgeon, persons who inject drugs, and/or men who have sex with men, particularly who are HIV positive
- a risk of severe clinical consequences, such as a patient with cirrhosis and acute superinfection of HCV
- higher likelihood of loss to follow-up, such as patients who may not be engaged in care for 3–6 months. (18)

The EASL guidelines say that immediate treatment of acute hepatitis C with DAAs improves clinical outcomes and was shown to be highly cost-effective compared with deferring treatment until the chronic phase of infection, but the ideal time point for starting therapy has not been firmly established. (16)

European AIDS treatment network (NEAT) and European Aids Clinical Society guidelines recommend a 4-week period to observe a potential HCV RNA decline of at least 2-log, after which the chance of spontaneous clearance becomes substantially higher. Without this 2-log decline, treatment can be initiated. (35)

Duration of treatment

The duration of IFN α and pegIFN-α treatment in hepatitis C virus infected patients is not strictly defined. Generally, treatment is recommend for 24 weeks, (36) but different studies showed good results with 4–24 weeks treatment.

Belgium a multicenter prospective study assessed the efficacy of subcutaneous interferon α-2b (IFN) 5 million units daily for 8 weeks, this study confirmed that treatment of acute hepatitis C with IFN for 8 weeks prevents chronicity. (37)

Randomized controlled trial in Japan showed that short-term (4 weeks) IFN treatment of patients with acute hepatitis C may be associated with satisfactory results, if initiated at an early stage of the disease. (38)

The duration of pegIFN-α treatment in HCV-mono-infected patients has been 24 weeks (39), however, 12 weeks of treatment has also been used successfully in observational studies, with cure rates of 72% and 74%. (40) (41) In a recent large, randomized controlled trial, no difference in response rates between 24 weeks of pegIFN-α and 12 weeks of pegIFN-α (with or without ribavirin) was observed and this study concluded that the only predictor of SVR was a rapid viral response at week 4. (31)

The ideal duration of treatment of acute hepatitis C with IFN-free regimens also remains unknown.

Three trials were performed with the fixed-dose combination of sofosbuvir and ledipasvir in patients infected with genotype 1. The SVR rates were: 93% (13/14)

after 4 weeks of treatment in injection drug users, (23) 77% (20/26) after 6 weeks of treatment in HIV-positive individuals, (24) and 100% (20/20) after 6 weeks of treatment in HIV-negative, non-injection drug users. (25) (16)

The combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir administered for 8 weeks yielded a 97% SVR rate in patients with acute or recent hepatitis C in the TARGET-3D study. (26)

As shown in the study from Austria interferon-free DAA regimens (including 34% pan-genotypic regimens) yielded 100% SVR12 in HIV/acute hepatitis C individuals if treatment durations similar to chronic hepatitis C are applied. (42)

AASLD/IDSA guidelines say that there are emerging data on the treatment of acute HCV infection with shortened courses of all-oral, DAA regimens compared to chronic hepatitis C therapy, but as yet, there are insufficient data to support a particular regimen or treatment duration. (18)

Similar according to EASL recommendations the ideal duration of treatment of acute hepatitis C with IFN-free regimens remains unknown, but according some trials EASL suggest that patients with acute hepatitis C should be treated with DAA combinations for 8 weeks, pending additional data establishing the ideal treatment regimen and duration. (16)

Key summary

Individuals with untreated hepatitis C infection have an approximate fivefold increase in all-cause mortality and a twentyfold increase in liver-related mortality. (17) Clinically, many acute hepatitis C patients are asymptomatic accordingly creating problems of adequate early diagnosis. (6)

Early control in the acute phase of hepatitis C infection can shorten disease duration and infectivity, to prevent chronicity and progression to advanced liver disease and to avoid eventual therapeutic non-response in the later stages of chronic hepatitis C.

In different studies several predictors of spontaneous viral clearance are described, but none of these parameters accurately predicts spontaneous resolution at the individual level.

The high rates of adverse events with IFN based therapy have led to delays in treatment initiation in acute infections which results in ongoing transmission. Clinical signs in patients or changes in laboratory tests cannot predict the efficacy of acute hepatitis C interferon based antiviral therapy.

In recent years the development in hepatitis C virus infections antiviral therapy is remarkable, though in contrast to chronic hepatitis C, a standard treatment has not been identified in the acute phase of the disease yet. DAAs are highly effective and safe, but expensive, therefore many countries defer treatment to advances stages of fibrosis. Future trials will need to investigate if even shorter therapies might be sufficient in some patients with acute hepatitis C, which would reduce the overall costs of antiviral drugs. The availability of new DAAs will result in more cured patients and can prevent new infections, thereby might help to reach the WHO goal of HCV elimination by 2030.

However it is not easy to predict when the chances of spontaneous clearance outweigh the effects of treatment.

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