ABSTRACT

Both human immunodeficiency virus (HIV) and hepatitis C (HCV) are globally infecting millions of people. Since these viruses are both transmitted through blood-blood contact the rate of coinfection is as high as 30% and among iv drug users in the Western world 70%. In the Netherlands, 8% of HCV-infected patients are coinfected with HIV. After the successful introduction of antiretroviral therapy (HAART) the survival of patients with HIV has increased considerably. Coinfection leads to accelerated progression of liver cirrhosis and liver failure but conflicting evidence exists about the effect of HCV on the natural course of HIV. Four randomised controlled trials have shown that treatment with pegylated interferon plus ribavirin leads to an overall sustained viral response (SVR) rate between 27 and 44%. Divided by genotype the SVR is between 14 and 38% in genotype 1 (and 4) while between 53 and 73% for genotype 2 and 3. These percentages are calculated based on an intention-to-treat analysis. Although lower than in HCV-monoinfected patients this is much higher than achieved with conventional interferon. However, coinfected patients with genotypes 2 and 3 also need to be treated for 48 weeks in contrast to monoinfected patients. As the number and severity of side effects is low, coinfected patients now have a substantially better option for treatment.

KEYWORDS

Hepatitis C, human immunodeficiency virus, treatment, viral kinetics

INTRODUCTION

Hepatitis C virus (HCV) is a global health problem with an estimated 170 million people (3% of the total population) infected with this virus worldwide. In the United States nearly four million and in Europe more than five million people are infected with hepatitis C. At least 20% of these patients are expected to develop cirrhosis of the liver and approximately 25% of them will eventually die from hepatic failure or require liver transplantation. At the end of 2003 the human immunodeficiency virus (HIV) had infected an estimated 37.8 million people worldwide causing devastating economic, social and cultural problems. HIV (a retrovirus) and HCV (a flavivirus) are both RNA viruses. Both viruses are transmitted through blood-blood contact while transmission of HIV is much more effective through sexual intercourse than HCV. Coinfection among patients is as high as 30% both in Europe and the United States. The group of patients most at risk in the Western world is iv drug users, where the prevalence of coinfection is as high as 80 to 90%. Among 6000 HIV positive patients in the Netherlands only 8% have HCV antibodies. Due to a widespread needle exchange and education programme the rate of coinfection is lower than in other parts of Europe. Since the introduction of highly active antiretroviral therapy (HAART) in 1996, the survival of patients with HIV has increased considerably. The mortality caused by opportunistic infections has declined shifting the focus of treatment to cardiovascular and liver-related pathology. Coinfection of HCV and HIV is leading to long-term complications of liver disease such as cirrhosis, liver failure and hepatocellular carcinoma. In this subgroup of patients it is becoming a serious problem with a high morbidity.
and currently the leading cause of death among coinfected patients. In recent years, with the introduction of pegylated interferon, the treatment of hepatitis C has undergone major changes. The enhanced bioavailability leading to a prolonged serum half-life, allowing once-weekly administration, results in a higher sustained virological response (SVR) than with conventional interferon. An SVR is defined as an undetectable HCV-RNA (<50 U/ml) at 24 weeks of follow-up after 48 weeks of treatment.

In a recent publication by Vrolijk et al., an excellent overview of the current treatment modalities for hepatitis C (non-coinfected) infected patients was given. Recently a few trials have been published on the treatment of hepatitis C in coinfected patients. The focus of this paper will be on the current available knowledge of virological interaction, viral kinetics and treatment in coinfected patients.

**Virological Interaction Between the Two Viruses**

The progression of hepatitis C monoinfection to cirrhosis and hepatocellular carcinoma is known to be slow, taking decades to develop. This depends on individual variables such as duration of infection, age at time of infection, male sex, amount of alcohol consumption, metabolic disorders and HIV coinfection.

**Effects of HIV infection on the natural history of liver cirrhosis**

Multiple studies have examined the effects of HIV infection on the natural history of chronic hepatitis C infection. This is mostly studied in patients with haemophilia since HAART only became widely available eight years ago. An advantage of studying rates of progression in patients with haemophilia is that the date of HCV exposure is often known. Patients with haemophilia, coinfected with HCV and HIV, develop hepatic decompensation or liver failure more frequently than haemophiliacs with hepatitis C only (8 and 14% vs 0 and 1%).

Graham et al. performed a meta-analysis of eight studies looking at histological proven cirrhosis (n=4) or decompensated liver disease (n=2) or both (n=2) in both iv drug users and patients with haemophilia. The combined adjusted relative risk (RR) was 2.14 (95% CI 1.15-3.97) demonstrating that coinfected patients progress faster to hepatic cirrhosis. Also the risk of decompensated liver disease increased sixfold. Other authors have shown that coinfection leads to a higher rate of hepatocellular carcinoma and that progression to liver failure is shortened to six to ten years. One explanation for this faster progression could be the immune compromised state of these patients. Bonnacini has shown in a summary of six previous articles that the rate of progression is inversely correlated to the CD4 count. A CD4 cell count lower than 500 cells/mm³ is associated with an increased risk for advanced fibrosis (OR 3.2, 95% CI 1.1-9.9). The accelerated progression of fibrosis is more significant among patients with lower CD4 counts. It can also be postulated that the difference in progression rate in hepatitis C is caused by the different HCV genotypes. However, two large studies have shown no effect of HCV genotype on fibrosis progression. A further two studies show that genotype 1 is closely associated with more severe histological liver damage and an increase in liver-related deaths.

**Effects of HIV and HAART on HCV load**

It is known that HCV/HIV coinfected patients have a higher HCV-RNA concentration than HCV-monoinfected patients. Spontaneous clearance of HCV occurs in 20% of cases in monoinfected patients vs 5 to 10% for coinfected patients. The immune response to hepatitis C is important in clearing the virus from the blood. This is done by CD4+ T helper cells, cytotoxic T lymphocytes and production of interferon. With HIV infection CD4+ lymphocytes show defective proliferation and apoptosis resulting in an impaired host immune response to HCV-infected cells leading to a higher HCV-RNA concentration. As stated above, the amount of CD4 cells is a prognostic variable for progression to liver cirrhosis. Therefore the effect of highly active antiretroviral therapy (HAART) on disease progression is interesting. Given the fact that HAART increases the number of CD4+ T cells (immune reconstitution), it can be postulated that progression to liver cirrhosis should halt. However, it is known that the total HCV-RNA load in untreated patients does not correlate with progression of liver cirrhosis. There are conflicting data on this immune reconstitution phenomenon. A retrospective study in France shows a favourable effect of protease inhibitor (PI) therapy on the progression of liver fibrosis. A total of 63 patients were treated with PIs compared with 119 PI-naïve patients. The cirrhosis rates were 2 vs 5%, 5 vs 18% and 9 vs 27% (p=0.0006) calculated at 5, 15 and 25 years, respectively. This effect was not seen in patients on nucleoside-based regimes only. An observational study by Qurishi et al. based on a twelve-year follow-up showed in a Kaplan-Meier analysis that patients treated with HAART have a lower liver-related mortality. Recently, Marina-Barjoan et al. showed that treatment with HAART had a favourable effect on liver fibrosis in coinfected patients. These observations favour the early initiation of antiretroviral therapy in coinfected patients to stimulate immune reconstitution and thus viral suppression leading to slower progression of liver disease. Interestingly, HAART-treated patients have a significantly greater increase in HCV-RNA load than patients treated with antiretroviral therapy (only nucleosides) or untreated patients. In contrast, Martin-Carbonero et al. found that immune reconstitution...
caused by antiretroviral therapy has no effect on the accelerated progression of liver fibrosis. In the later studies HCV-RNA load was found to increase after initiation of HAART and it steadily increase over time. These observations raise questions about the possible mechanism of antiviral therapy halting progression of liver cirrhosis. Many questions still remain to be answered.

Effects of HCV on HIV
Conflicting results have also been reported about the effect of chronic hepatitis C on progression of the natural history of HIV infection. Together with two early studies Greub et al. showed in the Swiss cohort that HCV/HIV-coinfected patients progressed faster to AIDS and death than patients with HIV infection only. The authors also noted a blunted CD4 cell response after initiation of HAART. In contrast, in a prospective study of 1995 HIV-positive patients in the USA, no difference was detected in progression to an AIDS-defining illness, progression to a CD4 cell count below 200/μl or survival between coinfected or HCV-negative patients. Moreover no difference was detected in the probability of experiencing a CD4 cell count increase of more than 50 cells/mm³ between coinfected and HCV-negative patients one, two and three years after initiation of HAART. Three more studies, European and American, also showed no difference in increased progression to an AIDS-defining illness or death between HCV positive or negative patients. Soriano et al. concluded in their recent review that HCV might act as a co-factor in HIV-positive patients by immune stimulation and possibly CD4 depletion causing a blunt response to antiretroviral therapy. However, they observed that the evidence was really poor.

VIRAL KINETICS

Lessons learned from viral kinetics in HIV have generated an enormous amount of research into HCV dynamics. HCV has a high replication rate of 1 x 10¹⁴ virions/day and a half-life of only three hours. Viral load levels of HCV remain relatively stable over time but are higher in HIV-infected patients. The decline in HCV-RNA after initiation of interferon (INF) and ribavirin treatment on both monoinfected and coinfected patients shows a biphasic pattern (figure 1). This first phase is rapid and occurs within 24 to 48 hours after the start of treatment. At that time the viral production and release of HCV is blocked. This reflects the sensitivity of the virus to interferon. The second phase is slower and more variable in time, reflecting the rate of immune-mediated clearance of HCV-infected cells. In genotypes 2 and 3 the slope in the first and second phase is steeper than for genotypes 1 and 4 resulting in a higher SVR after treatment. SVR after treatment. With conventional interferon dosing needs to be frequent because of the short serum half-life leading to large fluctuations in serum concentrations and therefore less steepness of the slope in both phases. The chemical modification of IFN by the covalent attachment of a polyethylene glycol (PEG) molecule results in a changed pharmacodynamic profile. The prolonged half-life results in a higher steady serum concentration of INF resulting in a steeper first and second phase. SVR after treatment. With conventional interferon dosing needs to be frequent because of the short serum half-life leading to large fluctuations in serum concentrations and therefore less steepness of the slope in both phases. The chemical modification of IFN by the covalent attachment of a polyethylene glycol (PEG) molecule results in a changed pharmacodynamic profile. The prolonged half-life results in a higher steady serum concentration of INF resulting in a steeper first and second phase. In coinfected patients the second phase seems to be less steep then in hepatitis C monoinfected patients. In contrast, two studies found no biphasic pattern in the majority of patients. Talal et al. administered conventional interferon monotherapy to 12 coinfected patients while achieving an early virological response in only three patients and a sustained virological response in one patient. Torriani et al. analysed a substudy of the APRICOT trial using pegylated interferon. No biphasic pattern was seen in nine out of ten patients coinfected with HIV and HCV. Recently a triphasic model of viral kinetics has been reported by Herrmann et al. In 34 patients with chronic hepatitis C, they found the typical first phase, a flattened or slowed second phase and a third phase in 61% of patients. The rate of decline during this third phase was significantly faster in those patients receiving ribavirin. Therefore, Herrmann hypothesised that this third phase may be a result of the addition of ribavirin leading to an upregulation of the immune system by ribavirin. In a recent study on the antiviral action of ribavirin in hepatitis C, this effect was not noted. The exact role of ribavirin in the viral decay needs further study.
The treatment of coinfected patients with HCV and HIV is challenging because of the low response rates to interferon and ribavirin. Therapy with interferon-based regimes are known to cause significant side effects such as flu-like symptoms and general symptoms of fatigue, malaise and weight loss.20,73,74 Psychiatric disorders, particularly depression, occur with an incidence of 20 to 30% affecting treatment adherence and sometimes requiring interferon dose reduction or discontinuation.75 Also autoimmune thyroiditis is reported to occur with a relative risk of 4.4.76 Therefore, patients should be carefully instructed about the occurrence of the above-mentioned side effects and followed up closely by their physicians.

Clinical trials
Recently two studies were published in the New England Journal of Medicine, one study in AIDS and one study in JAMA describing the result of peginterferon alpha-2a (Pegasys) or alpha-2b (Pegintron) with ribavirin in coinfected patients with HCV and HIV. Results of sustained virological response are summarised in table 1. The first is the APRICOT study (AIDS Pegasys Ribavirin International Coinfection trial),31 a randomised multicentre placebo-controlled blinded trial with 868 patients. Patients were assigned to either IFN alpha-2a plus ribavirin, PEG-IFN plus placebo or PEG-IFN plus ribavirin 800 mg. Irrespective of the genotype all patients were treated for 48 weeks followed by a 24-week observation period. All patients were HIV positive and had a CD4 cell count >200 cells/mm³ or between 100 to 199 cells/mm³ but than with a viral load of <5000 copies per ml. HAART had to be stable six weeks prior to entry with no changes expected within the next eight weeks. Thereafter changes in antiretroviral therapy were permitted. The SVR was 12% for the conventional interferon plus ribavirin group, 20% for the peginterferon group and 40% for the peginterferon plus ribavirin group. A multiple logistic-regression model resulted in two variables independently increasing the odds of achieving SVR. Those were an HCV genotype other than 1 (OR 3.37, CI 1.96-5.80) and baseline HCV-RNA levels of less than 800,000 IU (OR 3.56, CI 2.00-6.36). Parameters related to HIV infection, such as CD4 cell count and use of HAART, were not significant. Serious adverse events were low between 5 and 10% and not statistically significant among the treatment arms. Grade 4 haematological abnormalities were more frequent in the peginterferon groups. HCV treatment resulted in a slightly lower CD4 cell count but the percentage of cells was not affected.

The second trial is the ACTG 507124 trial which included 133 patients who were randomised to peginterferon alpha-2a (Pegasys) plus ribavirin in a dose-escalation schedule from 600 mg/day to 1000 mg/day or IFN plus dose-escalated ribavirin. As with the other trials a high percentage of genotype 1 was noted (78%). Patients had a well-controlled HIV infection with a mean CD4 count of 475 cells/mm³ and 86% received HAART. The overall SVR was 27% for the peginterferon group vs 12% for the conventional interferon group. Divided by genotype, differences in SVR with peginterferon were as expected, 73% for genotypes 2 and 3 while only 14% for genotype 1. Again side effects and adverse events were similar in both arms. Premature treatment discontinuation was 12% in both groups mainly because of depression and abnormal laboratory values. One case of clinical pancreatitis was noted leading to discontinuation of treatment. This patient was receiving didanosine. Similar to the APRICOT study no effect of HCV therapy on HIV progression was noted, with even a slight increase in the percentage of CD4 cells. Laguno et al.,26 in a small single-centre study, reported their results of peginterferon alpha-2b (Pegintron) plus

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**TREATMENT CHARACTERISTICS**

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<th>REFERENCE</th>
<th>SVR OVERALL</th>
<th>SVR PEG-INF + RIBAVIRIN</th>
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<tr>
<td></td>
<td>INF + RIBAVIRIN</td>
<td>PEG-INF + RIBAVIRIN</td>
</tr>
<tr>
<td>APRICOT23</td>
<td>12%</td>
<td>40%</td>
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<tr>
<td>ACTG24</td>
<td>12%</td>
<td>27%</td>
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<tr>
<td>Laguno et al.26</td>
<td>21%</td>
<td>44%</td>
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<tr>
<td>RIBAVIC25</td>
<td>20%</td>
<td>27%</td>
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ribavirin compared with interferon alpha-2b plus ribavirin in 95 patients. The dose of ribavirin was adjusted to body weight with 600 mg when the body weight was <60 kg, 1000 mg when it was 60 to 75 kg and 1200 mg when it was >75 kg. Both groups were treated for 48 weeks. Twenty-one patients (22%) with genotype 2 or 3 and a HCV-RNA load below 800,000 IU were treated with peginterferon (n=14) or conventional interferon (n=7) only for 24 weeks. Of the patients, 88% received antiretroviral therapy with a nucleoside reverse transcriptase inhibitor (NRTI) backbone. The patients, 82% received antiretroviral therapy with a nucleoside reverse transcriptase inhibitor (NRTI) backbone. The mean CD4 count was 560 x 10^6/l. The SVR was 44% in the peginterferon group and 21% in the interferon group with the SVR higher on treatment. In the peginterferon group genotypes 1 and 4 reached an SVR of 38 vs 53 and 47% for genotypes 2 and 3. No further remarks were made about the difference in duration of treatment in relation to the SVR. Altogether, 15% of the treated patients, nine in the peginterferon group and five in the interferon group, discontinued treatment because of serious adverse events such as flu-like symptoms, psychiatric disorders, lactic acidosis and severe anaemia. Haematological abnormalities required dose modification in 13% of patients with anaemia, while with neutropenia and thrombocytopenia this was 9 and 3%, respectively. In both treatment arms this did not reach statistical significance.

The RIBAVIC trial with 416 patients is a randomised controlled study of PEG-IFN alpha-2b (Pegintron) plus ribavirin 800 mg vs conventional IFN plus ribavirin 800 mg. The overall reported SVR was 27 vs 20% and varied with genotype; genotypes 1 and 4 being 17% and genotypes 2 and 3 being 44%. In the later genotypes no significant difference was noticed between the reached SVR between peginterferon and conventional interferon. Adverse events were similar in both groups and treatment discontinuation was as high as 30%. Symptomatic mitochondrial toxicity, including symptomatic hyperlactatemia, lactic acidosis and acute pancreatitis, occurred in 11 patients (3%) nine of whom were on peginterferon. All these patients received didanosine.

What can be learned?
Comparing these four trials is difficult because of the different brands of interferon, the baseline characteristics of the participants, sample size and the dose of ribavirin. Also the duration of treatment in genotypes 2 and 3 differed with 48 weeks in the APRICOT study while only 24 weeks for patients with a low HCV-RNA load in the study by Laguno et al. One interesting observation is the wide range in reported SVR. It is not yet clearly understood why the overall SVR in the APRICOT trial and the study by Laguno is 40 to 44 vs 27% in the RIBAVIC and ACTG trials. One explanation might be the difference in black patients between the different trials (33% in the ACTG trial vs 10% in the APRICOT trial while no numbers are mentioned in the other two trials). The brand of interferon does not explain the differences because both the higher and the lower SVR were achieved with both peginterferons. Currently a head-to-head study with both Pegasys and Pegintron (IDEAL study) is ongoing, but results will not become available for years. Another point is the difference in dosing regime of ribavirin. In the ACTG study a dose-escalated range is used because of fear for haematological side effects caused by ribavirin. The investigators also allowed the use of haematological growth factors. Laguno et al. used much higher doses of ribavirin up to 1200 mg (weight based) without reporting more adverse haematological events while not using granulocyte colony stimulating factor or erythropoietin. In chronic hepatitis C monoinfection the preferred dose of ribavirin is weight-based 1000 to 1200 mg/day. Recently, the PRESOC study was published by Nunez et al. treating coinfected patients with peginterferon alpha-2a and ribavirin 1000 to 1200 mg for 12 or 18 months for genotypes 1 and 4, and 6 or 12 months for genotypes 2 and 3. An overall viral response (ITT) after 48 weeks of treatment of 63% was reported with viral response of 50 and 44% for genotypes 1 and 4, respectively. Data on the impact of extended periods of therapy on SVR are not yet available. Exclusion criteria as mentioned above were also used in this study, only patients with higher CD4 counts of >300 cells/μl were accepted for treatment. The authors conclude that proper selection of patients, good monitoring and compliance and higher doses of ribavirin lead to an SVR in coinfected patients approaching those of HCV-monoinfected patients. Therefore, in view of the low reported haematological side effects, the optimal treatment dose of ribavirin appears to be 1000 to 1200 mg/day weight-based, especially in patients infected with genotypes 1 and 4.

The concept of an early virological response (EVR) published by Davis et al., defined as a 2 log10 decline in HCV-RNA load or undetectable levels of HCV-RNA at week 12 of therapy, safely predicts those patients who will reach SVR and those who will not. Patients who fail to achieve an EVR will not clear the virus and will not reach a SVR. So they are being treated with peginterferon unnecessarily, at a high cost and at risk considering the possible adverse events. Treatment is therefore stopped at week 12. In the APRICOT, ACTG and RIBAVIC trials this stopping rule is confirmed with only two out of 85 patients, none of 63 patients and one of 159 patients, respectively, not achieving an EVR at 12 weeks but reaching a sustained virological response at the end of treatment. In the four mentioned studies exclusion criteria applicable as contraindications to treatment were signs of decompensated liver cirrhosis, a major depression and signs of an autoimmune disease. Also, if patients had a CD4 count below 100 per mm³, anaemia, thrombocytopenia or low neutrophil counts they were not eligible for treatment.
Therefore, these patients should only be treated cautiously with peginterferon and ribavirin, and monitored closely. Another important issue is the interaction between ribavirin and antiretroviral therapy. Ribavirin, a nucleoside analogue, is known to inhibit mitochondrial polymerase gamma and to promote the intracellular conversion of didanosine to its active metabolite thereby leading to an increased and cytotoxic level of didanosine.79 The clinical syndrome of mitochondrial toxicity is symptomatic hyperlactataemia, lactic acidosis and pancreatitis. There is accumulating evidence warning against the concomitant use of didanosine and ribavirin.79,80 Although not reported in the APRICOT trial, the other three trials confirm that this combination leads to the clinical syndrome of mitochondrial toxicity. The same mechanism of action can account in vitro for other nucleoside analogues such as zidovudine and stavudine but this has so far not been proven to be clinically significant.79,82

In conclusion, patients with HVC genotype 1 and HIV coinfection treated with PEG-IFN plus weight-based ribavirin 1000 to 1200 mg/day can achieve an overall SVR between 27 to 44% as compared with standard IFN plus RBV. These sustained virological response rates are lower compared with the SVR in patients only infected with HCV. Although side effects are numerous and therapy is demanding for both patients and physicians, treatment with peginterferon and ribavirin is currently the best option for coinfectected patients. For genotypes 2 and 3, in contrast to monoinfected patients, a duration of therapy of 48 weeks is currently advised. The most common side effects of treatment are flu-like symptoms and depression, but this does not usually lead to treatment discontinuation. Adverse events are mild to moderate and can be treated with dose modification or with the use of haematological growth factors.

Where do we stand?

So where do we stand in treating hepatitis C and HIV coinfectected patients? Over the last years knowledge about viral kinetics, viral interaction and treatment in coinfectected patients is accumulating rapidly. This results in a better virological insight into how these viruses interact and in how to treat this subgroup of patients safely and successfully. There is still debate about the exact impact of HCV on the natural course of HIV and about the effects of HAART on HCV-RNA levels. In contrast, it is clear that coinfection with HIV leads to a faster progression of liver cirrhosis in hepatitis C infected patients. With numbers of patients increasing, it is vital that better treatment options are found.

The current optimal treatment strategy is pegylated interferon in combination with ribavirin for 48 weeks. There is still debate about the optimal dose of ribavirin in view of liver toxicity. The right time to start treatment is another key question to be resolved in the near future. What is emerging from these studies is that patients are eligible for treatment when they have moderate disease meaning a CD4 cell count above 200 cells/mm\(^3\), a stable regime of HAART without didanosine and signs of portal fibrosis or more (but not decompensated liver disease) on liver biopsy. There is still debate about when to start treatment in coinfectected patients with no signs of fibrosis or only showing signs of inflammation. According to the British guidelines\(^5\) there are two options, namely defer treatment and repeat a liver biopsy in two to three years time or start treating hepatitis C. Considering the increased progression rate to cirrhosis and fibrosis in coinfectected patients some experts in the field advocate starting hepatitis C treatment in this category of patients as soon as possible preferably before starting HAART. On the other hand cure rates are low, side effects often occur and only one treatment modality is currently available. International standards are currently not available. It is generally agreed that a CD4 cell count lower than 200 cells/mm\(^3\) is a contraindication for hepatitis C treatment and that first the effect of HAART should be awaited. Also patients with decompensated liver cirrhosis are not candidates for treatment because peginterferon is contraindicated in this subgroup of patients. Treatment modalities are changing rapidly. Analogue to the antiretroviral therapy in HIV patients, new nucleoside analogues and protease inhibitors are being developed. They will be introduced into clinical practice within the coming years.

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