

TREATMENT OF CHRONIC C HEPATITIS IN HIV INFECTED PATIENTS

Manuela Curescu

REZUMAT

Afectarea hepatică produsă de hepatita cronică cu virus C a devenit una din cauzele principale de deces printre pacienții infectați cu HIV, și ca rezultat al utilizării terapiei antiretrovirale extrem de eficiente. Din pacienții infectați cu HIV din Europa și America de Nord, aproximativ o treime prezintă și hepatită cronică cu virus hepatitic C. Deoarece hepatita cronică C progresează mult mai rapid în prezența coinfecției cu HIV, iar riscul hepatotoxicității antiretroviralelor este crescut în prezența unei hepatite C subiacente, terapia asocierii HIV/HCV a devenit o prioritate la pacienții coinfecțați.

Cuvinte cheie: terapie antiretrovirală HAART, Peginterferon, Ribavirină

ABSTRACT

Liver disease caused by chronic hepatitis C virus (HCV) has become one of the leading causes of death among HIV-infected patients, as a result of the wide use of potent antiretroviral therapies. Around one third of HIV-positive patients in Europe and North America have chronic hepatitis C. Since HCV-related liver disease progress much faster in the setting of HIV infection and the risk of liver toxicity using antiretroviral drugs is increased in the presence of underlying chronic hepatitis C, treatment of this condition has become a priority in co-infected patients.

Key Words: HAART (highly active antiretroviral therapy), Peginterferon, Ribavirin

INTRODUCTION

Both hepatitis C virus (HCV) and HIV infections are global public health problems. More than 42 million people are estimated to be living with HIV worldwide, while HCV infection is found in 2-3% of the world population (about 175 million).¹ Overall nearly 10 million people are co infected with both HIV and HCV.² (Fig. 1)

Transmission of either HCV or HIV is frequent throughout parenteral exposure to blood and blood products, with HCV being 10 times more infectious than HIV.

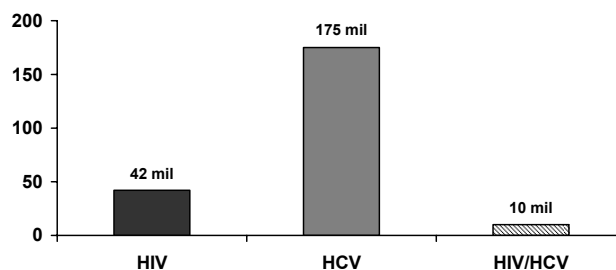


Figure 1. Global distribution of hepatitis C virus and HIV infections.

The distribution of HCV genotypes in the HIV population reflects the main route of HCV transmission. Genotype 1b accounts for more than two thirds of post-transfusion HCV infections. Genotype 1a and 3a are much more frequent among IV drug users. HIV accelerates HCV liver disease, especially when HIV-associated immunodeficiency progresses.^{3,4}

Hepatitis C virus (HCV) is found in 30% of HIV-positive people. HCV-related liver disease is a leading cause of morbidity and death among HIV-infected people, where classical opportunistic complications of severe immunodeficiency have declined dramatically as a result of the use of potent antiretroviral therapy (HAART = highly active antiretroviral therapy). There is probably a greater risk for accelerated liver disease

Department of Infectious Diseases, Victor Babes University of Medicine and Pharmacy, Timisoara

Correspondence to:
Manuela Curescu, 5A Banul Maracine Str., Timisoara, Tel. +40-722-786508,
Fax +40-256-201026
Email: manuela.curescu@dominet.ro

Received for publication: 25 Jan. 2006. Revised: 11 Dec. 2006.

in subjects with HIV/HCV coinfection. HIV/HCV coinfection can result in a higher incidence of HIV drug-related liver toxicity and the mechanisms for this are not precisely understood. Interactions between drugs used to treat HCV and HIV can cause toxicity in unpredictable ways.

MECHANISMS OF ACTION OF RIBAVIRIN AND INTERFERON

Dosing of Ribavirin differs by HCV genotype.⁵ Ribavirin treatment duration also depends on genotype: 24 weeks for genotypes 2 and 3 and 48 weeks for genotypes 1 and 4. A viral load that is undetectable six months after stopping therapy is considered a sustained viral response (SVR). For genotype 1, SVR is attained by approximately 47% of those with a high viral load (more than 800,000 IU/ml) and by 65% of those with a lower viral load. For genotypes 2 and 3, the proportion of patients attaining SVR is similar regardless of viral load, approximately 84%.⁶

The mechanism of action for Interferon alfa is complex as it exerts its effect at multiple sites. It augments cellular immunity by:

- Increasing Th 1 immunity;
- Up-regulation of human leukocyte antigen (HLA) class I (A, B, C) and II (DR, DP, DQ);
- Enhancing innate immunity (NK).

TH 1 promotes cytotoxic T-lymphocyte activity against viruses. Interferon-alfa has also anti-proliferative effects.

Ribavirin is a synthetic guanosine analogue, which inhibits IMPDH (inosine-5'-monophosphate dehydrogenase), nucleic acid (RNA and DNA) synthesis, and has activity against some RNA and DNA viruses. It has a weak or inhibitory effect on HCV replication and the way it works in a synergistic manner with interferon-alfa may be an immunomodulatory effect.

There are 21 HCV-specific cytotoxic T lymphocytes (CTL) and nine HCV targets. It seems essential for HCV clearance that liver CTLs simultaneously target multiple HCV proteins, with many CTLs targeting even single peptide epitopes. When there are attacks at many sites, each site needs many different T cells, due to plasticity and the existence of many mutations.

In natural immunity, CD4 T cells determine the strength and type of immune response by secreting cytokines and the TH 1 cytokines stimulate CTLs. In therapeutic immunity, the augmentation of the TH1 response may be an important component of induced HCV clearance.

INTERACTIONS BETWEEN ANTIRETROVIRAL DRUGS AND HCV MEDICATION

Liver complications that may occur with use of nucleosides and nucleotides include the effect of treatment of hepatitis with Lamivudine (3TC) and Tenofovir (TDF) and steatosis and increased liver enzymes with Zidovudine (ZDV). Elevated liver enzymes are not uncommon with the non-nucleoside reverse transcriptase inhibitors (NNRTI). For the protein inhibitors (PI), increase in alanine aminotransferase (ALT) has been documented with Indinavir (IDV), Nelfinavir (NFV), Ritonavir (RTV) and Saquinavir (SQV). An increase in unconjugated bilirubin has also been noted with IDV. Hyperbilirubinemia has been seen with IDV as well as case reports of portal vein thrombosis. Hepatitis has been seen with RTV, IDV, NFV and SQV.

An increased hematological toxicity is seen due to interactions between Interferon/Ribavirin and antiretroviral therapy. Erythropoietin helps patients with anemia maintain the ribavirin dose, with better quality of life and better safety. For patients with neutropenia, it is unknown at what level to introduce granulocyte-colony stimulating factor (GCSF).

Patients on nucleoside reverse transcriptase inhibitors (NRTI) and Ribavirin have an increased risk of mitochondrial toxicities (MT), pancreatitis or lactate above 7.4 mmol. Patients with HIV/HCV co-infection should avoid Didanosine (ddI), since Ribavirin can enhance the intracellular concentrations of phosphorylated Didanosine (ddI) metabolites and result in a higher risk of toxicity.⁸ Several cases of pancreatitis and/or lactic acidosis have been reported when Ribavirin is given together with ddI. Most recently, cases of hepatic decompensation have been reported in subjects receiving Ribavirin with ddI.

For the next five years, interferon-based therapy is expected to remain the mainstay of HCV treatment. Lower doses of Interferon/Ribavirin might be achieved with newer combinations, which may benefit HIV co-infected patients by increasing effectiveness.

HEPATOTOXICITY AND HAART

The liver is the conduit for biotransformation of almost all drugs. The phase 1 oxidative reactions of CYP450 have the potential to create harmful metabolites, while the phase 2 conjugation reactions may protect the liver from active metabolites. Deficiencies in glutathione conjugations can

contribute to drug-induced liver disease. This may be predictable or unpredictable. These reactions are dose-dependent and host-independent, occur with high incidence and have early onset. Unpredictable drug reactions are host-dependent, have a low incidence and are not dose-related. The majority of drug reactions in HIV patients are unpredictable: here the drug metabolite affects immunologic response as well as exerting direct toxicity.

Host-mediated hypersensitivity reaction is one type of unpredictable side effect. Symptoms include fever and rash; eosinophilia is also possible. There are two hypotheses pertaining to mechanisms of hypersensitivity reactions. The Hapten hypothesis asserts that reactive metabolites covalently bind to a macro-molecule. This is perceived as a neoantigen, which stimulates both arms of the immune system, leading to hepatic sensitization. The “danger hypothesis” adds to the understanding: it asserts that the right environment is necessary for the reaction. The immune response to the perceived neoantigen only occurs if the “danger signal” is seen.

Host-mediated “idiosyncratic” metabolism accounts for the vast majority of reactions. These host differences in drug metabolism may lead to an excess of reactive drug metabolites or perhaps deficiencies of certain enzymes that are necessary to break down the drug.

Nucleoside reverse transcriptase inhibitors (NRTI) have been associated with mitochondrial function (MT). Impaired mitochondrial function can lead to a decrease in free fatty acid oxidation. Free fatty acids accumulate and are metabolized to triglycerides, leading to hepatic steatosis. There are two patterns of steatosis:

- Macro-vesicular steatosis: hepatocytes contain a single large vacuole of fat, which fills up the cell, pushing the nucleus to the periphery;
- Micro-vesicular steatosis, where hepatocytes are filled with numerous small lipid vesicles which leave the nucleus in the center of the cell.

Short and long-term success of HAART in HIV/HCV – co-infected patients is limited by an increased risk of hepatotoxicity. Multiple studies have demonstrated that underlying hepatitis C is an independent predictor of liver enzyme elevations after initiating HAART.

STAGING OF CHRONIC HEPATITIS C IN HIV/HCV CO-INFECTION

The time interval between HCV acquisition and development of liver cirrhosis is significantly

shortened in co-infected patients. On average and within 10-15 years of initial HVC infection, 15-25% of HCV/HIV co-infected patients develop liver cirrhosis.⁹ (Fig. 2)

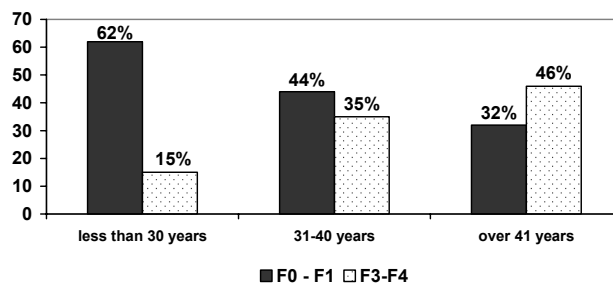


Figure 2. Liver fibrosis according to age in HCV/HIV coinfected patients.

Recent evidence suggests that the immune restoration that follows the use of antiretroviral therapy might reverse the unfavorable course of hepatitis C in co-infected patients. The data available suggest that HAART has a favorable impact on the future course of hepatitis C in co-infected patients.¹⁰⁻¹²

HIV CANDIDATES FOR HCV THERAPY

All HIV-infected patients should be screened for HCV antibodies; in cases of negative HCV-antibodies, but positive HCV-RNA, the cause mainly is due to severe cellular immune suppression.¹³⁻¹⁵ All patients with repeatedly elevated aminotransferase levels should be tested for HCV load and HCV genotype.

Since the response to HCV therapy is dependent on the CD4 count, this should be prescribed only when the CD4 count exceeds 350 cells/ μ L. In subjects with CD4 count between 200-350 cells/ μ L and already under long-term antiretroviral therapy, the decision to treat HCV might be considered taking into account the severity of liver disease, the extent of suppression of HIV replication, the HCV genotype and viral load.^{16,17}

Therapy should be deferred in patients with less than 200 CD4 T-cells/ μ L, since the response rate is very low in these patients.^{18,19}

Patients with liver decompensation (ascites, gastrointestinal bleeding, and hepatic encephalopathy) should not be treated, given the higher risks of serious side effects of Peginterferon/Ribavirin. However, patients with compensated cirrhosis (Child-Pugh class A) must be treated, since they will benefit the most from HCV clearance.

Following 2002 NIH Consensus Conference recommendations, patients with normal liver enzymes might benefit from HCV therapy, particularly those infected with genotypes 2 or 3. In drug naïve individuals

with HCV/HIV co-infection, HCV should be treated first, if the CD4 count is greater than 350 cell/ μ L.^{20,21}

TREATMENT RESULTS IN HCV/HIV CO-INFECTED PATIENTS

The combination of Peginterferon α 2a and Ribavirin is effective and well tolerated in patients with HCV/HIV co-infection. A standard dose of Peginterferon α 2a of 180 mcg/week plus Ribavirin 1000 mg/day produce higher virological response rates at the end of treatment than the combination of Peginterferon α 2a plus Ribavirin 800 mg/day (43% vs. 29%).^{22,23} In patients infected with genotype 1, the overall end-of-treatment virological response rate was 33%; in those harboring HCV genotypes 2 or 3, the overall end-of-treatment virological response rate was 50%.²⁴ (Fig. 3)

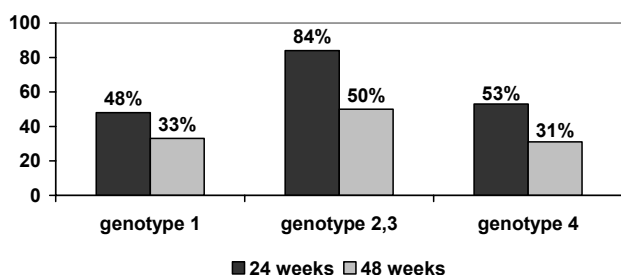


Figure 3. HCV/HIV co-infection- virological response at week 24 and 48.

The reasons why anti-HCV therapy provides a poorer response in HIV-infected patients are numerous:^{25,26}

- Use of lower-than-optimal doses of Ribavirin;
- Less activity of anti-HCV therapy in the setting of HIV-related immune dysfunction;
- More advanced liver fibrosis stage;
- Higher rate of steatosis (alcohol, nucleoside analogs);
- Unfavorable HCV virological features (high HCV-RNA titers);
- Lower initial HCV-RNA clearance;
- More frequent relapses after treatment discontinuation;
- Higher rate of treatment withdrawals due to side effects;
- Lower drug compliance.

MONITORING THE THERAPY

Kinetic studies suggest that HCV clearance after beginning therapy with Peginterferon plus Ribavirin may be delayed in the setting of HIV infection.²⁷ (Fig. 4)

Patients with high HCV loads may show a good early

virological response, but may not reach undetectable viral load at week 24, despite which they will clear HCV much later.²⁸ (Fig. 4a) There is a second phase of clearance of HCV-RNA in patients on prolonged HCV therapy that accounts for the steadily destruction of infected hepatocytes. (Fig. 4b) A slower decay in HCV-RNA could explain why early discontinuation of therapy might result in higher relapse rate.^{29,30}

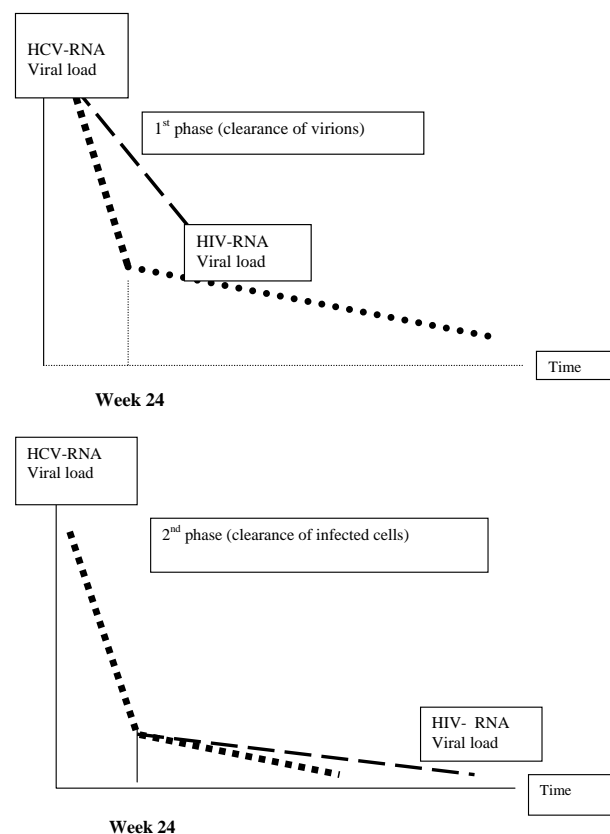


Figure 4. Hepatitis C virus kinetics under interferon therapy and influence of HIV infection. a). early phase; b). second phase.

CONCLUSIONS

The use of Peginterferon plus Ribavirin improves the rate of SVR in HIV infected patients with chronic hepatitis C and therefore should be considered the best treatment choice.^{31,32}

REFERENCES

1. Alter M. Epidemiology of Hepatitis C. Hepatology 1997;(Suppl):62-5.
2. Soriano V, Nunez M, Camino N, et al. Treatment of hepatitis C in HIV infected patients. Hepatology Rev 2004;2:59-71.
3. Backus, LI, Boothroyd D, Deyton LR. HIV, hepatitis C and HIV/ hepatitis C virus co-infection in vulnerable populations. AIDS. 2005;19(suppl 3):S13-9.
4. Backmund M, Meyer K, Von Zielonka M, et al. Treatment of chronic hepatitis C infection in injecting drug users. Hepatology 2001;34:188-93.
5. Pol S, Thiers V, Losbaum J, et al. Changing distribution of HCV genotypes in Europe in the last decades. J Hepatol 1994;21(Suppl):13-7.

6. Sylvestre DL. Approaching treatment for hepatitis C virus infection in substance users. *Clin Infect Dis*. 2005;41(Suppl 1):S79-82.
7. Lafeuillade A, Hittinger G, Chapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. *Lancet* 2001;357:1803.
8. Perez- Olmeda M, Rios P, Nunez M, et al. Virological characteristics of hepatitis C virus infection in HIV-infected patients with chronic hepatitis C: implications for treatment. *AIDS* 2002;16:493-5.
9. Benhamou Y, De Martino V, Bochet M, et al. Factors affecting liver fibrosis in HIV and hepatitis C virus coinfecting patients: impact of protease inhibitor therapy. *Hepatology* 2001;34:283-7.
10. Garcia-Samaniego J, Rodriguez M, Berenguer J, et al. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am J Gastroenterol* 2001;96:179-83.
11. Martin-Carbonero L, Benhamou Y, Puoti M, et al. Incidence and predictors of severe liver fibrosis in HIV-infected patients with chronic hepatitis C – a European collaborative study. *Clin Infect Dis* 2004;38:128-33.
12. Cribier B, Rey D, Schmitt C, et al. High hepatitis C viremia and impaired antibody response in patients coinfecting with HIV. *AIDS* 1995;9:1131-6.
13. Beld M, Penning M, Van Putten M, et al. Low levels of HCV-RNA in serum, plasma and PBMCs of IDUs during long antibody-undetectable periods before seroconversion. *Blood* 1999;94:1183-91.
14. George S, Gebhardt J, Klinzman D, et al. Hepatitis C viremia in HIV-infected individuals with negative HCV antibody tests. *J Acquir Immun Def Syndr* 2002; 31:154-62.
15. Gao B, Hong F, Radaeva S. Host factors and failure of interferon treatment in hepatitis C virus. *Hepatology* 2004; 39:880-90.
16. Zeuzem S. Heterogeneous virologic response rates to interferon-based therapy in patients with chronic hepatitis C: who responds less well? *Ann Intern Med* 2004;140:370-81.
17. Soriano V, Garcia- Samaniego J, Bravo R, et al. Interferon alfa for the treatment of chronic hepatitis C in patients infected with HIV. Hepatitis-HIV Spanish study group. *Clin Infect Dis* 2002;35:585-91.
18. Mauss S, Klinker H, Ulmer A, et al. Response to treatment of chronic hepatitis C with interferon alfa in patients infected with HIV-1 is associated with higher CD4+ cell count. *Infection* 1998;26:16-9.
19. Soriano V, Puoti M, Sulkowski M, et al. Care of patients with hepatitis C in HIV coinfection. Updated recommendations from the HCV-HIV International panel. *AIDS* 2004;18:1-12.
20. NIH Consensus Development Conference Statement: Management of Hepatitis C. *Gastroenterology* 2002;123:2082-99.
21. Perez-Olmeda M, Nunez M, Romero M, et al. Pegylated interferon alfa 2b + ribavirin as therapy for chronic hepatitis C in HIV-infected patients. *AIDS* 2003;17:1023-8.
22. Voigt E, Schulz C, Mauss S, et al. Factors related to outcome of treatment with pegylated interferon alfa 2a + ribavirin in HCV/HIV coinfecting patients. 2nd IAS Conference on HIV Pathogenesis and Treatment. Paris 2003;976.
23. Ballesteros A, Franco S, Fuster D, et al. Early HCV dynamics on peginterferon and ribavirin in HIV/HCV coinfection: indications for the investigation of new treatment approaches. *AIDS* 2004;18:59-66.
24. Fuster D, Planas R, Gonzalez J. Results of a study of prolonging treatment with pegylated interferon-alpha2a plus ribavirin in HIV/HCV coinfecting patients with no early virological response. *Antiviral Therapy* 11(4):473-482. 2006.
25. Moreno L, Quereda C, Moreno A, et al. Pegylated interferon alfa 2b + ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. *AIDS* 2004;18:67-73.
26. Manns M, McHutchinson J, Gordon S. Peginterferon alfa 2b + ribavirin compared with interferon alfa 2b + ribavirin for initial treatment of chronic hepatitis C. *Lancet* 2001;358:958-65.
27. Fried M, Shiffman M, Reddy R. Peginterferon alfa 2a + ribavirin for chronic hepatitis C infection. *N Engl J Med* 2002;347:975-82.
28. Toriani F, Ribeiro R, Gilbert T, et al. HCV and HIV dynamics during HC treatment in HIV/HCV coinfection. *J Infect Dis* 2003;188:1498-507.
29. Buti M, Valdes A, Sanchez-Avila F, Esteban R, et al. Extending combination therapy with peginterferon alfa 2b + ribavirin for genotype 1 chronic hepatitis C late responders. *Hepatology* 2003;37:1226-7.
30. Neumann A, Lam N, Dahari H, et al. Hepatitis C viral dynamics in vivo and the survival efficacy of interferon alfa therapy. *Science* 1998;282:103-7.
31. Pawlotski JM. Use and interpretation of virological tests for hepatitis C. *Hepatology* 2002;36(Suppl):65-73.
32. Fleming CA, Tumilty S, Murray JE, et al. Challenges in the treatment of patients coinfecting with HIV and hepatitis C virus: need for team care. *Clin Infect Dis*. 2005;40(Suppl 5):S349-54.