Eur J Med Res (2005) 10: 43-45

MANAGEMENT OF CHRONIC HEPATITIS C IN HIV-CO-INFECTED PATIENTS

RESULTS FROM THE FIRST INTERNATIONAL WORKSHOP ON HIV AND HEPATITIS CO-INFECTION

2nd – 4th December 2004, Amsterdam, Netherlands

Abstract: About 30% of HIV-positive individuals are concomitantly infected with HCV within the United States and Europe. Approximately 50 to 90 % of persons who acquired HIV from injecting drugs are co-infected with HCV. In these dually infected individuals the presence of each viral infection may impact the natural course of the other one, and worsening of associated liver disease and complications within this population are frequent. The management of *chronic hepatitis C (cHC) in HCV-HIV-co-infection* has become a major challenge, as possible interactions with *antiretroviral therapy* (ART), increased risk of special side effects, as well as compromises in adherence of patients, who already take several drugs, have to be taken into account. Treatment strategies to fight HCV-infection have been essentially ameliorated during the past three years in using *pegylated interferon alpha* (PegIFN alpha) combined with *ribavirin* (Rbv). There is hope that the beneficial therapeutic outcome in HCV-mono-infected individuals may be at least partly translated into successful treatment of dually infected patients too. However, the stepwise amelioration of therapeutic options and strategies does actually not yet result in equal anti-HCV response rates for co-infected compared to HCV-mono-infected persons.

The 1st International Workshop on HIV and Hepatitis Co-infection 2004, was initiated to face the severe clinical problems which arise from viral hepatitis and HIV dual infection. The organising committee was headed by *J. K. Rockstroh, University of Bonn, Germany,* as chair and *M. Sulkowski, John Hopkins University, USA*, as co-chair of the meeting, in which more than 300 researchers and physicians from various European and US locations participated. This report summarizes some results on epidemiology, pathogenesis, viral interactions, and treatment of chronic hepatitis C in HIV- infected individuals.

Key words: HIV, HCV, liver disease, chronic hepatitis C (cHC), antiretroviral therapy (ART), pegylated interferon alpha (PegIFN alpha), ribavirin (Rbv), 1st International Workshop on HIV and Hepatitis Co-infection 2004, epidemiology, pathogenesis, viral interactions, treatment of chronic hepatitis C

METHODOLOGICAL ISSUES IN CLINICAL EPIDEMIOLOGY OF HCV-HIV-CO-INFECTION

Hepatitis C is a global health problem. WHO estimated the number of carriers in 1999 within a range of 170 to 400 millions worldwide, while it has to be taken into account that the situation in China is up to now not at all explored, as M. Sulkowski stated in his lecture on epidemiology. The incidence rate of hepatitis co-infection in cohorts of HIV-infected people reflects the different spread of the disease in various parts of the world (Table 1).

HCV clearance is lower, which was shown in the Baltimore Cohort of HIV-infected drug users, where 722 of 1667 persons who showed up with antibodies to hepatitis C were persistently infected.

Within the CAESAR study the sources of infection for HIV-positive persons with acute hepatitis C were reported as 15 % by sexual transmission, 10 % by transfusion, 60 % by needle sharing in intravenous drug users (IVDU`s), others in 5 %, and unknown in 10 %, respectively. Sulkowski supposed that the high percentage of sexual transmission might be due to false reported by IVDU- patients. Vertical transmission of HCV was found to be at 3.8 fold higher risk in HIV-infection.

A. Phillips, London, UK, focussed on methodological issues in clinical epidemiology of co-infection and warned of false conclusions made in cohort studies. This refers for example on true versus reported alcohol consumption. From the results of a study from Piroth et al published in AIDS 1998, the risk of alcohol intake has been underestimated, and this bias can-

Table 1. Hepatitis Co-infection in various cohorts of HIV-infected individuals.

cohorts	observation time	hepatitis B	hepatitis C
ICONA	1997 – 2000	7.2 %	46.2 %
Ivory Coast	2004	9.0 %	1.0 %
EuroSIDA	1994 – 2003	9.0 %	34.0%
John Hopkins	1996 – 2002	6.0 %	46.0 %

not be overcome by increasing sample size. Also the reported data of the Swiss Cohort study [1], which reported a higher rate of progression to AIDS or death as an independent risk factor for HCV-infected persons, were not reproducible within the EuroSIDA and the John Hopkins cohorts, respectively, where factors as CD4-cellcount status, prior AIDS-manifestations and use of ART have been controlled. Even if such characteristics could be measured, multivariable models cannot necessarily reliably discern the independent effect of HCV status.

Pathogenesis of HCV-HIV-co-infection

Main aspects of direct and indirect interactions between the two viruses have been summarized by *U. Spengler, Bonn*, Germany. Within a haemophiliac cohort differences in NK-cell expression in HCV-mono-infected versus HCV-HIV- co-infected persons were already described by Darby et al in 1997. In HIV- as well as HCV- infection a shift from Th1 (cytotoxic immune response) to Th2 (humoral immune response) occurs featuring in IL-4, IL-5, and IL-10 expression. In HCV, however, the IL-4 production occurs after stimulation with HCV core antigens. Increased markers of early apoptosis have been reported on CD4(+)/CD30(+) lymphocytes from patients with cHC by his group in 1999. HIV- as well as HCV- immunity was observed in long-term non-progressors (LTNP) responsive to HIV p24 antigen, and depletion of HCV-specific cells was seen in HIV-progressors. Munshi et al found in 2003 that HCV-epitope E2 and HIV- gp120 synergize to induce apoptosis in hepatocytes.

There are two different mechanisms which may trigger liver damage. If CD4-counts are high, increased inflammation activity can add to fibrosis. If CD4-counts are low the exhausted HCV-specific immune response leads to increased HC-viral replication. As an unspecific immune response is following HAART, where HCV-specific cells are not increased, it is suggested that HAART improves fibrosis.

Although HCV itself does not use co-receptors, it down-regulates CCR5, the co-receptor of HIV. While each additional inflammation is suspected to drive the natural course of HIV-infection forward, HCV-infection does obviously not, so there must be a counteracting mechanism. CCR5- antagonism may be one explanation, another one is that hepatitis G infection, which is frequently associated to HCV, acts competitively to HIV and thus slows down the course of HIV-infection.

Challenges in HIV and Hepatitis C Co-infection

Jens Lundgren, Copenhagen, Denmark, summarized that in general response rates to anti-HCV-treatment are lower in HIV-infected persons and discontinuations of treatment are obviously higher than in HCV-mono-infected patients. As possible causes of failure to respond he listed

- In general higher HC-viral load in HIV-positive persons
- a qualitative defect in cellular immune responses (TH1-like HCV-specific immune response)
- more toxicities arising from co-medications
- a different mode of action of pegylated interferon and ribavirin

This all may add to lower reproducibility of failure to respond and in poor responder identification. Other obstacles for successful treatment include the higher risk of anaemia in HIV-positive persons, the general higher risk in treating cirrhotic patients, the fact that IFN-alpha works less in patients with low CD-counts, the requirement of stable life style, and more need of support by the medical institutions.

The interplay between replication of HBV and HCV and immune responses has to be elucidated regarding viral factors as the source of virus in blood (Laskus et al., Blood 2004) and factors of the immune system as cellular and/or humoral components (Herrero-Martinez, JMV 2004), as well as compartments and reservoirs (Graham et al., Hepatology 2004).

It can be regarded as a paradox that fibrosis and ALT elevation are a result of immune activation, but that HIV and/or immune deficiency accelerates fibrosis. Other unanswered questions are if co-infection is a specific risk for hepatitis C to become chronic and/or will a co-infected person present first in term of shortest way to go for the virus. Finally, clinical consequences of long-term inhibition of the cytochrom P450 system as done by ART are not yet investigated.

The concern if decreasing CD4-counts under lymphocyte-suppressive anti-HCV combination therapy could lead to higher risk for opportunistic infections is attenuated by the fact that within former findings in KS-patients treated with IFN-alpha no increased rate of opportunistic infections occurred. It is probable that the lympho-suppressive effect of IFN and ribavirin is over-compensated in anti-HCV therapy of co-infected patients by the general antiretroviral effect of IFN on HIV. Potthoff et al. showed in a poster presentation of the meeting that relative lymphocyte counts were stable during the treatment duration and absolute lymphocyte counts stabilized after first decline to their base values, while HIV-RNA-levels decreased.

State of the Art in Treatment of Chronic Hepatitis C in HIV-co-infected Patients

Results from recent trials with pegylated interferon and ribavirin show lower sustained response rates and higher discontinuation rates than reported in HCV mono-infected patients [2]. Table 2 summarizes the results of actual therapy studies performed in HCV-HIV dually infected patients treated with a combination of pegylated IFN-alpha and ribavirin [3-9].

Due to unfavourable baseline HCV virologic features and HIV-related immune deficiency, it is often necessary to treat once diagnosed. When possible, concomitant HAART should be avoided and a close monitoring is recommended to keep patients on full therapy. Relapse in genotype 2/3 (g 2/3) patients may be avoided if treatment duration is extended to 48

Table 2. Results of trials with pegylated interferon and ribavirin in HIV/HCV-coinfected patients.

Type of pegylated IFN	duration of treatment	ribavirin dose(mg/d)	n	EOT to adverse events	SVR	withdrawals due	author
alfa-2b	g1: 48w g2/3: 24w	800	68	27(40%)	19 (28%)	10(15%)	Perez-Olmeda 2003
alfa-2b	g1: 48w g2/3: 24w	800	72	33(46%)	19(26%)	12(17%)	Voigt 2003
alfa2b	all g: 48w	800	205	NA	55(27%)	77(38%)	Perronne2004
alfa2a	all g: 48w	600 from w12:1000	66	27(41%)	18(27%)	8(12%)	Chung 2004
alfa2a	all g: 48w	800	286	47%	15(40%)	12%	Torriani 2004
alfa2b	all g: 48w	800	35	14(40%)	11(31%)	6(17%)	Moreno 2004
alfa2b	g1: 48w g2/3: 24w	800-1200	52	52%	44%	9(17%)	Laguno 2004

g = HC-genotype, EOT = virological response (negative for HCV-RNA) at end of treatment, SVR = virological response 24 weeks after end of treatment, NA = not available

weeks [4], while studies with only 24 weeks duration of therapy reported higher relapse rates for patients with g 2/3 [6, 7].

V. Soriano, Madrid, Spain, summarized actual treatment guidelines of cHC in HIV-co-infected patients. Decision to initiate anti-HCV-therapy as well as recommendations of monitoring response have been subject to two recent international expert panels [10, 11]. The therapy of choice is analogue to HCV-mono-infected persons the combination of pegylated interferon and ribavirin. Anti-HCV-treatment should be recommended primarily on the basis of fibrosis (F1-F4) or fibrosis markers in combination with raised serum aminotransferases and positive HCV-RNA tests. Ideal candidates for anti-HCV therapy are patients with CD4-cell counts of higher than 350 cells per mcl and less than 50.000 HIV-RNA copies per ml, with or without HAART. In patients with less than 350 CD4-cells per mcl HAART should be optimised before starting anti-HCV-therapy, and if CD4-cell counts are lower 100 to 200 per mcl, they should receive HAART first to increase CD4-cell counts before initiating treatment of cHC. As also priorly shown in HCV-mono-infection, early virologic response (EVR) – defined as more than 2 log decrease in serum concentrations of HCV-RNA copies after 12 weeks – is predictive for the chance of sustained response, and treatment can be stopped at week 12 if no EVR is achieved. The treatment duration of all genotypes is 48 weeks in HCV-HIV-co-infection. The concomitant use of didanosine and ribavirin should be avoided. Combination of zidovudine or stavudine with ribavirin may increase toxicity, and closer safety monitoring is warranted.

References

1. Greub G, Ledergerber B, Battegay M et al. Clinical progression, survival and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection. Lancet 2000; 356: 1800-1805
2. Manns MP, McHutchinson JG, Gordon SC et al. Peginterferon alfa2b in combination with ribavirin compared to interferon alfa2b plus ribavirin for initial treatment of chronic hepatitis C: results of a randomized trial. Lancet 2001; 358: 958-965
3. Chung R, Andersen J, Volberding P, et al. A randomized contolled trial of peg-interferon-alfa2a + ribavirin versus interferon-alfa2a + ribavirin for chronic hepatitis C virus infection in HIV-coinfected persons: follow-up results of ACTG A5071. 11th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA, USA, Feb 8-11, 2004: abstr 110
4. Torriani FJ, Rockstroh J, Rodriguez-Torres M, et al. Final results of APRICOT: a randomized partially blinded international trial evaluating peg-interferon-alfa2a + ribavirin in the treatment of HCV in HIV/HCV coinfection. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, USA, Feb 8-11, 2004: abstract 112
5. Perronne C, Carrat F, Bani-Sadr F, et al. Final results of ANRS HCO2-Ribavic: a randomized controlled trial of pegylated interferon-alfa2b + ribavirin in the treatment of chronic hepatitis C in HIV-coinfected patients. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, USA, Feb 8-11, 2004: abstr 117LB
6. Voigt E., Schulz C, Mauss S, et al. Factors related to outcome of treatment with pegylated interferon-alfa2b (PEG-INF) + ribavirin (RBV) in HCV/HIV-coinfected patients. 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, France, 2003: abstr 976
7. Perez-Olmeda M, Nunez M, Romero M, et al. Pegylated interferon-alfa2b + ribavirin as therapy for chronic hepatitis C in HIV-infected patients. AIDS 2003; 17: 1023-28
8. Moreno L, Quereda C, Moreno A et al. Pegylated interferon-alfa2b + ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. AIDS 2004; 18: 67-73
9. Laguno M, Murrilas J, Blanco JL et al. Pegylated interferon-alfa2b plus ribavirin compared with interferon-alfa2b plus ribavirin for treatment of HIV/HCV coinfected patients. AIDS 2004; 18: F27-F36
10. Soriano V, Sulkowski M, Bergen C et al. Care of patients with chronic hepatitis C and HIV coinfection: recommendations from the HIV/HCV International Panel. AIDS 2002; 16: 813-24
11. Soriano V, Puoti M, Sulkowski M et al. Care of patients with hepatitis C and HIV-coinfection. AIDS 2004; 18: 1-12

Address for correspondence:
Dr. Gudrun Tossing
Essex Pharma GmbH, Munich
Tannenstrasse 15/15a
D-42653 Solingen, Germany
Phone/Fax: +49 (0) 212 / 586153
E-mail: gudrun.tossing@essex.de