**Low-dose IL-2 Therapy Reduces HCV RNA and HBV DNA: Case Report**

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**Abstract.** Background: Patients with concomitant hepatitis C (HCV) and B (HBV) infection are difficult to treat due to lack of medicines that control these viral infections and the high risk of hepatocellular carcinoma. Currently, there are insufficient data regarding the therapeutic effect of interleukin-2 (IL-2) during chronic viral infection, but this cytokine has shown antineoplastic activity and may have also an antiviral effect. Case Report: We present the case of a 44-year-old patient with hemophilia A, HBV and HCV related compensated liver cirrhosis (Child-Pugh A) with several zones in the liver, highly suspicious for hepatocellular carcinoma. The patient was treated with low-dose intermittent subcutaneous IL-2 immunotherapy, followed by standard therapy with pegasys and copenus. During 23 months’ follow-up, no tumour progression occurred, and the patient remained in Child-Pugh A stage. The initial HCV and HBV loads were significant (538,207 IU/ml) and minimal (825 copies/ml), respectively. The patient was treated with intermittent subcutaneously applied low-dose IL-2 cycles for ten months. HBV DNA and HCV RNA were undetectable 3 months after the last IL-2 cycle. After cessation of IL-2 therapy, the patient received standard antiviral treatment with pegasys and copenus. Nine months later, a slight reactivation of viruses was observed: HBV DNA was 18,600 copies/ml and HCV RNA was 58 IU/ml. Twenty-three months after the last IL-2 treatment (at the time of writing), the patient is alive and in a good clinical condition. Conclusion: The decrease of HBV and HCV nucleic acids during immunotherapy with IL-2 predicts a possible new therapeutic option for these chronic viral infections.

**Case Report**

We present the case of a 44-year-old patient with hemophilia A, established when he was 7 years old, with many traumas, surgical interventions and blood transfusions in the past. In 1996, HBV and HCV infections were detected: HbsAg (+), anti-HCV (+), anti-HDV (–). The consumption of alcohol until 2005 was significant, at an equivalent of 200-250 ml pure ethanol daily. In 2005, elevated liver enzymes and liver cirrhosis were established. Ultrasound investigation revealed...
liver cirrhosis, portal hypertension and splenomegaly. X-Ray investigation (09/2006) and later gastroscopy (01/2008) excluded esophageal varices. In September 2006, several zones in the liver highly suspicious for HCC were established by ultrasound and computer tomography – three hypodense zones in the VI liver segment (approximately 15 mm) and one zone in the VII liver segment (approximately 12 mm). Histological verification of the lesions and local therapy were not possible due to hemophilia. No other primary tumor was found despite different methods of investigation. Different tumor markers assessed were as follows: cancer antigen CA19-9, carcinoembryonal antigen and prostate-specific antigen were normal; alpha-fetoprotein (α-FP) 13.6 ng/ml, slightly elevated (normal range <10 ng/ml). The zones suspicious for HCC were treated as HCC. We proposed the patient to undergo immunotherapy with IL-2 (proleukin, Chiron) which he accepted. As local treatment was not an option due to the concomitant disease, we started subcutaneous applications. We applied 3 million IU IL-2 for 6 consecutive days. Therapy was started in November 2006 for six monthly cycles. Due to personal reasons, IL-2 therapy was discontinued for three months, and in August 2007, a seventh, and last cycle was given. The therapy was well tolerated, without significant toxicity. The only side-effects were chills, temperature increase, muscle and joint pains and redness at the injection site.

From January 2008 until July 2008, the patient was approved for standard therapy with interferon and ribavirin, *i.e.* treatment with copegus (800 mg/daily) and pegasys; initially the dose of pegasys was 180 μg weekly for 1 month, thereafter due to hematological toxicity, namely a decrease in white blood cells, platelets and hemoglobin, the dose was diminished to 90 μg/weekly and later even to 60 μg/weekly. Computer tomography in September 2007 and June 2008 showed stable disease for HCC 9 months after the last IL-2 cycle. The tumor marker α-FP returned to normal levels immediately after the start of therapy, and remained normal during IL-2 therapy and thereafter (Figure 1). Gamma-glutamyl aminotransferase transiently decreased during IL-2 therapy (Figure 2) and alanine aminotransferase remained decreased (Figure 3). White blood cells and hemoglobin did not change during IL-2 therapy but decreased after initiation of pegasys and copegus (Figures 4 and 5). Platelets showed a tendency to decrease during follow-up, but a more significant decrease was registered after initiation of therapy with pegasys and copegus (Figure 6). Serum levels of HBV DNA and HCV RNA were measured by real-time quantitative PCR and RT-PCR. The initial HCV viral load was significant, while the HBV viral load was very low. Three months after the last IL-2 application, serum levels of HBV DNA and HCV RNA were below the detection limits of 300 copies/ml and 50
IU/ml, respectively. A decrease in liver enzymes also occurred. Nine months after cessation of IL-2 cycles and in spite of the standard antiviral treatment, viral recurrence was observed (Table I). Twenty-three months after the last IL-2 treatment (at the time of writing), the patient is alive and in a good clinical condition.

Discussion

We have treated a patient suspected of having HCC with s.c. IL-2 application. The timing of reactions to IL-2 treatment is shown in the Figures and the Table. Most importantly, HBV DNA and HCV RNA dropped to undetectable levels (Table I). Inhibition of viral replication was observed after the start of IL-2 therapy and before initiation of interferon and ribavirin therapy. Based on this and on the timing of the reactions shown in the Figures and the Table, we believe that these results were not related to alcoholism or to the standard treatment for HBV and HCV. A similar regime of low-dose IL-2 was found to be effective in HIV infection (12, 13). IL-2 is an important player in the regulation of innate and adaptive immunity. This cytokine exerts pleiotropic actions and directly stimulates T and B lymphocytes, natural killer cells and monocytes (14). IL-2 therapy in cancer patients increases the levels of proinflammatory cytokines and lymphocyte cytotoxicity (15, 16). These mechanisms are important in antiviral immunology against HBV and HCV (17). Antiviral treatment of chronic HBV infection with Peg-interferon alpga and chronic HCV infection with Peg-interferon alpha and ribavirin can reach 30-60% efficacy (18, 19). These partial therapeutic successes in chronic HCV and HBV infection call for the development of new therapeutic schemes and new drugs. New interferon molecules, allowing interferon alpha application once in a fortnight, were unable to increase significantly the therapeutic efficacy. Application of protease and polymerase inhibitors, drugs with direct suppression of HBV and HCV replication, is an additional therapeutic option, but their activity can disappear once viral resistance occurs (20). Our observation of the change and disappearance of HBV and HCV replication shortly after immunotherapy with IL-2 highlights an interesting therapeutic option.

**Table I. Changes in viral replication.**

<table>
<thead>
<tr>
<th>Date of treatment</th>
<th>HBV DNA</th>
<th>HCV RNA</th>
<th>Therapy</th>
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</thead>
<tbody>
<tr>
<td>Nov. 2006</td>
<td>825 copies/ml</td>
<td>538, 207 IU/ml</td>
<td>First IL-2 therapy</td>
</tr>
<tr>
<td>Sep. 2007</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Last IL-2 therapy</td>
</tr>
<tr>
<td>Jan. 2008</td>
<td>N.D.</td>
<td>N.D.</td>
<td>Start pegasy+copegus</td>
</tr>
<tr>
<td>Feb. 2008</td>
<td>&lt;300 copies/ml</td>
<td>N.D.</td>
<td>Pegasy+copegus</td>
</tr>
<tr>
<td>Jun. 2008</td>
<td>18,600 copies/ml</td>
<td>58 IU/ml</td>
<td>Pegasy+copegus</td>
</tr>
</tbody>
</table>

N.A., Not analyzed; N.D., Not detectable.
References


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