Chronic hepatitis C: new diagnostic tools and therapeutic strategies
Damen, M.

Citation for published version (APA):
Chapter 8

**WHAT IS THE MEANING OF AN ANTI-HCV POSITIVE, HCV-PCR NEGATIVE TEST RESULT?**

M. Damen¹, E.P. Mauser-Bunschoten², H.T.M. Cuypers¹,
H.M. van den Berg², P.N. Lelie¹

¹The Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Viral Diagnostic Department, Amsterdam, The Netherlands

²Van Creveldkliniek (Dutch National Hemophilia Centre), University Hospital Utrecht, Utrecht, The Netherlands

ALT value was significantly higher in the group with serum that tested anti-HCV positive, HCV-RNA negative at baseline, were scheduled for further analysis. In 40/40 patients (100% 95% CI 96-100%) the second yearly control PCR was also negative. In 39/40 patients (97.5% 95% CI 91-100%) with a third control visit, the PCR was negative at all three visits and in 25/25 patients (100% 95% CI 95-100%) with a fourth control visit, the PCR was negative at all four visits.

From this study we may conclude that the anti-HCV positive, HCV-RNA negative patient usually reflects resolved HCV infection, because this pattern persists in almost 90% of the patients during 2-3 years follow-up with yearly measurements. Furthermore, median ALT levels were significantly higher in patients with detectable HCV-RNA than those without after this long-term follow-up period. The slightly elevated median ALT level at time-to-time in patients with anti-HCV positivity, PCR negativity may be explained by residual damaged hepatocytes in a subgroup of patients being in a relatively early stage after viral clearance. Years after resolved infection even HCV infections have been found to disappear in some patients (unpublished observations). In other studies, the presence of HCV-RNA in plasma, with or without ALT elevation, was associated with histological evidence of hepatic inflammation and fibrosis.¹ We recommend that patients with an anti-HCV positive, HCV-RNA negative test result are followed-up yearly. After 2 years, follow-up visits can be less frequent, if this pattern persists. This policy is required for reliable counselling of patients.
Hepatitis C (HCV) infection is correlated with chronic hepatitis and development of liver cirrhosis, especially if besides HCV antibodies also HCV-RNA is detectable in plasma with PCR\(^1\). However, less is known about the prognosis of anti-HCV positive patients without detectable HCV-RNA. These patients might have resolved the HCV infection, but theoretically they could have either HCV-RNA levels below the detection limit of the HCV-PCR assay or intrahepatic HCV-RNA\(^2\).

Before the introduction of anti-HCV testing of blood donors and solvent detergent (SD) virus inactivation in the preparation of blood products, hemophilia patients were at high risk for HCV infection\(^3\). At the Dutch National Hemophilia Centre, patients were routinely tested for indices of hepatitis C infection after informed consent, at yearly visits from 1992. Between 1992 and 1995, 363 patients (born between 1919-1994) were tested at a first visit for HCV-antibodies, HCV-RNA and ALT level. A subset of 185 patients, who had been tested on at least two occasions and who had not received IFN treatment before the first visit, was selected for this analysis. Due to the long study period, second-generation as well as third-generation anti-HCV screenings assays (Enzyme Immuno Assay (EIA), Abbott) and confirmation assays (Recombinant Immunoblot Assay; RIBA HCV SIA, Chiron Corporation, Emeryville, CA) were used. An in-house developed cDNA-PCR\(^4\) as well as the HCV AMPLICOR assay (Roche Diagnostic Systems, Branchburg, NJ) with modified sample preparation\(^4\) were applied for HCV-RNA detection.

In the table, the follow-up data on the indices of HCV infection in the 185 patients are shown. At baseline, the median ALT value was significantly elevated in the groups with anti-HCV positivity, both with and without viremia. At the last (analyzed) visit, the median ALT value was significantly higher in the groups with viremia than those without viremia. Forty-eight patients who were anti-HCV positive, HCV-RNA negative at base-line, were selected for further analysis. In 43/48 patients (90%; 95% confidence interval (CI) 77-97%) the second yearly control PCR was also negative. In 39/40 patients (98%; 95% CI 87-100%) with a third control visit, the PCR was negative at all three visits and in 25/25 patients (100%; 95% CI 86-100) with a fourth control visit, the PCR was negative at all four visits.

From this study we may conclude that the anti-HCV positive, HCV-RNA negative pattern usually reflects resolved HCV infection, because this pattern persists in almost 90% of the patients during 2-5 years follow-up with yearly measurements. Furthermore, median ALT levels were significantly higher in patients with detectable HCV-RNA than those without after this long-term follow-up period. The slightly elevated median ALT level at base-line in patients with anti-HCV positivity, PCR negativity may be explained by residual damaged hepatocytes in a subgroup of patients being in a relatively early stage after viral clearance. Years after resolved infection even HCV antibodies have been found to disappear in some patients (unpublished observations). In other studies, the presence of HCV-RNA in plasma, with or without ALT elevation, was associated with histological evidence of hepatic inflammation and fibrosis\(^1^5\). We recommend that patients with an anti-HCV positive, HCV-RNA negative test result are followed-up yearly. After 2 years, follow-up visits can be less frequent, if this pattern persists. This policy is required for reliable counselling of patients.


Table:
HCV virology and ALT values in 185 Dutch hemophila patients with two or more yearly measurements.

<table>
<thead>
<tr>
<th>Base-line:</th>
<th></th>
<th>Last visit:</th>
<th></th>
<th>Follow-up period years</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>anti-HCV</td>
<td>PCR</td>
<td>ALT index&lt;sup&gt;a&lt;/sup&gt;</td>
<td>P&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>80</td>
<td>neg</td>
<td>neg</td>
<td>0.38 (0.14-1.57)</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>pos</td>
<td>neg</td>
<td>0.71 (0.23-4.19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5</td>
<td>pos</td>
<td>neg</td>
<td>1.62 (0.48-3.62)</td>
<td>0.0019</td>
</tr>
<tr>
<td>57</td>
<td>pos</td>
<td>pos</td>
<td>2.17 (0.48-3.62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>17</td>
<td>pos</td>
<td>neg</td>
<td>0.38 (0.18-11.36)</td>
<td>NS</td>
</tr>
</tbody>
</table>

<sup>a</sup> ALT index=measured ALT value/upper level of normal

<sup>b</sup> Mann-Whitney Test; difference in ALT index with anti-HCV negative / PCR negative group is tested; NS=not significant.

<sup>c</sup> 1/17 patients lost HCV-RNA spontaneously, in 16/17 patients PCR became negative after Interferon treatment.