Hepatitis C infection: the quest for new treatment strategies
Weegink, C.J.

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Development of myasthenia gravis during treatment of chronic hepatitis C with interferon-alpha and ribavirin

CJ Weegink\textsuperscript{1}, RAFM Chamuleau\textsuperscript{1}, HW Reesink\textsuperscript{1}, DSM Molenaar\textsuperscript{2}.

\textsuperscript{1}Department of Gastroenterology and Hepatology
\textsuperscript{2}Department of Neurology
Academic Medical Center
Amsterdam, The Netherlands

Case Report

Two weeks before his admission a 44 year old male truck driver fell down the stairs. Within a few days he had developed fluctuating double vision, difficulty in chewing and swallowing, and weakness of the arms and legs. By that time he had been treated for 15 months with interferon-alpha-2b (IFN) (3 million units sc., t.i.w.) and ribavirin (1000 mg daily) in a controlled clinical trial for chronic hepatitis C. Before starting this treatment the alanine aminotransferase (ALAT) was 71 U/L (upper limit of normal = 37 U/L), the HCV-RNA was positive (genotype 1a, 2.9 million copies (cps)/ml) and a liver biopsy had shown chronic persistent hepatitis with mild fibrosis. After initiating therapy he experienced increased fatigue. In the following 6 months he had lost 12 kg of weight. Hyperthyroidism was diagnosed and believed to be an autoimmune thyroiditis, frequently reported during IFN monotherapy. Subsequently, he became hypothyroid and treatment with 100 µg L-thyroxin daily was started. At that time the ALAT was normalised, but HCV-RNA remained detectable (2.2 million cps/ml). Because the thyroid disorder was not regarded as a severe adverse event, trial medication was continued.

On admission to the neurological department he was cachectic and dyspnoeic at rest. His speech was slurred; he had bilateral ptosis, weakness of head- and neck musculature and a tetraparesis. Further investigation revealed an elevated titre of acetylcholine receptor (AChR) antibodies (0.89 nmol/l; normal < 0.30 nmol/l), and electromyography was consistent with myasthenia gravis (MG). CT of the mediastinum showed no evidence of a thymoma. Treatment with pyridostigmine for MG was started and trial medication was stopped. Within a few days he needed artificial ventilation and prednisolone was added. Over the next 4.5 months his condition improved slowly. He was discharged to a stairless house. One and a half year later, the ALAT remained normal but the HCV-RNA was still detectable in the blood. He was euthyroid and without L-thyroxin medication, but dependent on prednisolone and pyridostigmine. He remained unable to return to work.

Multiple plasma samples were available since the start of the trial medication. These were tested for thyroid- and AChR antibodies (Table). Before treatment with the trial medication, none were detectable. After 6 months thyroid antibodies were evident. Elevated AChR antibody titre was first detected when he was admitted for MG. These findings suggest that both the autoimmune thyroiditis and the MG were induced by IFN/ribavirin treatment.

Table

<table>
<thead>
<tr>
<th>Time from onset of treatment (months)</th>
<th>Autoantibodies</th>
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<tbody>
<tr>
<td></td>
<td>Thyroid-colloid</td>
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<tr>
<td>Before (0)</td>
<td>-</td>
</tr>
<tr>
<td>(6)</td>
<td>±</td>
</tr>
<tr>
<td>Admission (15)*</td>
<td>+</td>
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<tr>
<td>Discharge (20.5)</td>
<td>+</td>
</tr>
<tr>
<td>(26.5)-now</td>
<td>-</td>
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</table>

*IFN/Ribavirin treatment was stopped at this time point
Chronic infection with hepatitis C virus has been associated with various autoimmune diseases, including MG, a neuromuscular disorder of autoimmune origin (1). More than half of the patients with chronic HCV treated with IFN develop auto-antibodies (2). Most commonly these are thyroid antibodies, associated with hyperthyroidism or hypothyroidism. Ribavirin monotherapy has not been associated with the development of auto-antibodies or autoimmune diseases (3). Development of MG, with elevated levels of AChR antibodies, has been reported in three patients treated with IFN monotherapy for chronic hepatitis C (4, 5, 6), until now, no cases of MG have been reported in patients treated with the combination therapy IFN/Ribavirin. However, it cannot be excluded that in our patient Ribavirin has potentiated the autoimmuno modulating effect of IFN.

Nowadays, many patients with chronic HCV are treated with combined treatments in clinical trials. We suggest that each patient should be monitored carefully for autoimmune phenomena, and that stopping the immunomodulating treatment should be considered, if an autoimmune disease develops and the patient is still HCV-RNA positive at that time.

References
