Serial changes of anti-HCV core titer in patients with chronic hepatitis C treated with peginterferon: a useful marker for outcome contributing to choice of an appropriate therapy

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Abstract

Serial measurements of ALT, HCV-RNA and anti-HCV core titer were made from the start of therapy in 19 patients undergoing treatment with peginterferon (including combined therapy with ribavirin) for chronic hepatitis C. Anti-HCV core titer in SVR patients in both the peginterferon and ribavirin combination therapy group and the peginterferon monotherapy group fell continuously from the start of therapy, with the rate of decrease reaching 50% at the end of therapy, and continued to fall after the therapy ended. In non-SVR patients, there was no clear decrease after the start of therapy, and the anti-HCV core titer rose after the end of therapy. In addition, as 12 of 13 SVR patients were EVR, it appears that shortening the therapy period can be considered for both peginterferon and ribavirin combination therapy and peginterferon monotherapy when the patient shows EVR and the anti-HCV core titer decreases continuously during therapy. By avoiding unnecessary continuous treatment, more appropriate peginterferon therapy methods and administration periods can be used when treating chronic hepatitis C in patients with background risk factors.

Key words: hepatitis C, peginterferon, ribavirin, anti-HCV core titer, side effects

Introduction

The outcomes in chronic hepatitis C therapy in Japan have improved markedly since the 2005 introduction of peginterferon therapy for patients who have serogroup 1 and high viral load. Patients that appear to have been cured through eradication of the virus now account for more than half of all cases of therapy. The administration period of peginterferon is usually 24 to 48 weeks, and the standard administration is a single subcutaneous injection each week. The advantage of this regimen is that the cold-like symptoms that appear as side effects are extremely mild, thereby improving adherence. Nonetheless, as with conventional interferon therapy, the frequency of serious side effects necessitates close and continuous monitoring.

We have previously reported cases of thyroid dysfunction during peginterferon administration²,³. In such cases, the patient was positive for thyroid autoantibodies, and while the primary disease of chronic hepatitis C was cured, reducing the period of peginterferon administration could have prevented thyroid dysfunction. The presence of a marker predicting final therapeutic efficacy as soon as possible after the start of therapy would be extremely useful in such patients, as it would allow unnecessary treatment to be discontinued and prevent the occurrence of side effects. Here, we investigated the relationship between serial changes in anti-HCV core titer and therapeutic efficacy during peginterferon treatment in order to determine whether anti-HCV core titer could be a marker for predicting the outcome of therapy for chronic hepatitis C.

Subjects and Methods

Subjects were 19 patients treated with peginterferon for chronic hepatitis C (Table 1). ALT, HCV-RNA and anti-HCV core titer
were measured at the start of therapy and were each measured once a month until the end of peginterferon treatment, and were subsequently measured at 6 months and 1 year after the end of therapy. In determining therapeutic efficacy, HCV-RNA continuously negative for 6 months or more from the end of therapy was taken to be sustained viral response (SVR), anything else was taken to be non-SVR. In addition, disappearance of HCV-RNA within 1 month of the start of therapy was taken to be early viral response (EVR), and patients in which HCV-RNA did not disappear were "null." Statistical analysis was performed using SPSS 17.0J for Windows (SPSS Inc., IL, USA). Student’s t-test were used to determine significant differences, and P values of less than 5% were considered significant.

The present study conformed to the guidelines of epidemiological studies devised by the Ministry of Health, Labor and Welfare, Japan, to prevent leakage of personal information, and were conducted for the purposes of social benefit.

Results

1. Clinical characteristics of patients treated with peginterferon and administration methods (Table 1)

Table 1. Patients with chronic hepatitis C treated with peginterferon in various methods

<p>| Group A: combination of peginterferon and ribavirin for high viral load |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>patient</th>
<th>sex</th>
<th>age [Yr]</th>
<th>immediately before the treatment</th>
<th>HCV-RNA (IU/mL)</th>
<th>duration</th>
<th>method at the start</th>
<th>time of HCV-RNA disappearance</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>54</td>
<td>69</td>
<td>2655</td>
<td>48 wk</td>
<td>Peginteron 100 μg/wk + Rebetol 800mg/day</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>67</td>
<td>120</td>
<td>3,300</td>
<td>48 wk</td>
<td>Peginteron 100 μg/wk + Rebetol 800mg/day</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>45</td>
<td>227</td>
<td>416.7</td>
<td>24 wk</td>
<td>Peginteron 100 μg/wk + Rebetol 800mg/day</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>61</td>
<td>122</td>
<td>242.4</td>
<td>48 wk</td>
<td>Peginteron 150 μg/wk + Rebetol 800mg/day</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>41</td>
<td>54</td>
<td>94.9</td>
<td>24 wk</td>
<td>Peginteron 100 μg/wk + Rebetol 800mg/day</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>41</td>
<td>40</td>
<td>1300</td>
<td>48 wk</td>
<td>Peginty 180 μg/wk + Copebas 600mg g/day</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>58</td>
<td>26</td>
<td>3600</td>
<td>44 wk</td>
<td>Peginty 180 μg/wk + Copebas 600mg g/day</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>57</td>
<td>76</td>
<td>1185</td>
<td>48 wk</td>
<td>Peginty 180 μg/wk + Copebas 600mg g/day</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>51</td>
<td>73</td>
<td>1900</td>
<td>48 wk</td>
<td>Peginty 180 μg/wk + Copebas 600mg g/day</td>
<td>null</td>
<td>non SVR</td>
</tr>
</tbody>
</table>

<p>| Group B: peginterferon monotherapy for low or middle viral load |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>patient</th>
<th>sex</th>
<th>age [Yr]</th>
<th>immediately before the treatment</th>
<th>HCV-RNA (IU/mL)</th>
<th>duration</th>
<th>method at the start</th>
<th>time of HCV-RNA disappearance</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>51</td>
<td>73</td>
<td>5000</td>
<td>24 wk</td>
<td>Peginty 180 μg/wk</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>71</td>
<td>43</td>
<td>2862</td>
<td>24 wk</td>
<td>Peginty 180 μg/wk</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>55</td>
<td>103</td>
<td>113.6</td>
<td>24 wk</td>
<td>Peginty 180 μg/wk</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>58</td>
<td>113</td>
<td>4769</td>
<td>24 wk</td>
<td>Peginty 180 μg/wk</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>45</td>
<td>183</td>
<td>39.9</td>
<td>24 wk</td>
<td>Peginty 180 μg/wk</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>52</td>
<td>10</td>
<td>4500</td>
<td>24 wk</td>
<td>Peginty 90 μg/wk</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>45</td>
<td>14</td>
<td>221.1</td>
<td>20 wk</td>
<td>Peginty 90 μg/wk</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>54</td>
<td>179</td>
<td>406</td>
<td>24 wk</td>
<td>Peginty 90 μg/wk</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>54</td>
<td>70</td>
<td>1100</td>
<td>28 wk</td>
<td>Peginty 180 μg/wk</td>
<td>null</td>
<td>non SVR</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>58</td>
<td>86</td>
<td>2157</td>
<td>24 wk</td>
<td>Peginty 180 μg/wk</td>
<td>null</td>
<td>non SVR</td>
</tr>
</tbody>
</table>

*discontinued for a side effect. ND: not detected, null: no disappearance, EVR: at one month. SVR: sustained viral response

The peginterferon and ribavirin combination therapy group (Group A) consisted of 9 patients (8 males, 1 female) with an average age of 52.8 years. Average pre-therapy ALT value was 90.0 IU/L, average pre-therapy anti-HCV core titer was 208.8 U, and most patients were serogroup 1 with high viral load. The peginterferon alone therapy group (Group B) consisted of 10 patients (6 males, 4 females) with an average age of 55.3 years. Average
pre-therapy ALT value was 87.4 IU/L. Average pre-therapy anti-HCV core titer was 254.3 U, and most patients were serogroup 1 or 2 with low to moderate viral load.

In Group A, there were 5 SVR patients and 4 non-SVR patients. Disappearance of HCV-RNA occurred as EVR in all 5 SVR patients. Disappearance of HCV-RNA in the 4 non-SVR patients was one each of EVR, temporary, after 5 months, and null. In Group B, there were 8 SVR patients and 2 non-SVR patients. Disappearance of HCV-RNA occurred as EVR in 7 of the 8 SVR patients and after 5 months in 1 patient. Disappearance of HCV-RNA in the 2 non-SVR patients was one each of null and after 2 months.

2. Comparison of serial changes of average anti-HCV core titer in SVR and non-SVR patients treated with combination therapy of peginterferon and ribavirin (Figure 1)

Anti-HCV core titer showed a gradual decrease following the start of therapy in both SVR and non-SVR patients. However, the rate of decrease was greater in SVR patients, reaching 50% at the end of therapy, with lower values than in non-SVR patients (p=0.1755). At 6 months after the end of administration, SVR patients showed even lower values, while the values increased in non-SVR patients with a significant difference between SVR and non-SVR (p<0.001).

3. Serial changes in average anti-HCV core titer in SVR patients treated with peginterferon monotherapy (Figure 2)

![Figure 1. Comparison of serial changes of average anti-HCV core titer during the course of combination therapy of peginterferon and ribavirin who displayed SVR and non SVR](image1)

![Figure 2. Serial changes of average anti-HCV core titer during the course of peginterferon monotherapy who displayed SVR](image2)
Anti-HCV core titer showed a gradual decrease after the start of therapy with a rate of decrease of 34% at the end of therapy, reaching 60% 1 year after the end of drug administration.

4. Serial changes in anti-HCV core titer in 2 patients who displayed non-SVR after treatment with peginterferon monotherapy (Figure 3)

Anti-HCV core titer until the end of therapy increased slightly and then decreased slightly in Patient 1, and decreased slightly and then increased slightly in Patient 2.

5. Comparison of serial changes in average ALT levels in SVR and non-SVR patients treated with combination therapy of peginterferon and ribavirin (Figure 4)

SVR patients showed higher values than non-SVR patients at the start of therapy, but in both groups they were almost normalized 1 month after the start of therapy and stayed normalized thereafter. At 6 months after the start of therapy the ALT levels in SVR patients were higher than in non-SVR patients (p=0.1459), and conversely, at the end of therapy, levels were higher in non-SVR patients than SVR patients (p=0.1538). Both groups showed normal levels at 6 months after the end of therapy.

6. Serial changes in ALT levels and anti-HCV core titer in a 55-year-old male who displayed SVR treated with peginterferon monotherapy (Figure 5)

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Figure 3. Serial changes of anti-HCV core titer during the course of peginterferon monotherapy in two patients who displayed non SVR (Group B, patients 1, 2)

Figure 4. Comparison of serial changes of average ALT level during the course of combination therapy of peginterferon and ribavirin who displayed SVR and non SVR
The patient showed EVR, being negative for HCV-RNA continuously from 1 month after the start of therapy. ALT levels, however, rose after the start of therapy and abnormal levels persisted until the end of therapy, returning to normal 6 months after the end of therapy. Anti-HCV core titer increased immediately after the start of therapy but subsequently decreased, showing a sharp decrease from 6 months after the end of therapy and decreasing to 40% at 1 year after the end of therapy.

7. Serial changes in ALT level in 2 patients who displayed non-SVR after treatment with peginterferon monotherapy (Figure 6)

Slight abnormalities in ALT levels persisted in Patient 1 until the end of therapy, while ALT levels in Patient 2 became normal after the start of therapy and remained almost normalized until 1 year after the end of therapy.

Discussion

Peginterferon maintains an active therapeutic range in blood for longer than conventional interferons due to its pharmaceutical characteristics.
and its antiviral action is reinforced when administered in combination with ribavirin. Patients are generally examined once a week, meaning that the interval between examinations is longer than with conventional interferon therapies and there is all the more need for meticulous checks for side effects. Peginterferon is typically administered in combination with ribavirin to serogroup 1 patients with a high viral load for 48 weeks, and is administered as monotherapy for 24 weeks to serogroup 2 patients or patients with low viral load.

Anti-HCV core is an antibody against HCV structural proteins that allows reliable diagnosis of HCV infection. The immunoradiometric assay (IRMA) is widely used, with the antibody titer expressed as units (U), and 1 U or more is taken as a positive result. This reflects active replication of HCV in infected individuals, but as individuals infected with HCV in the past also give positive results, the presence or otherwise of viremia in anti-HCV core-positive patients is problematic in epidemiological surveys. We previously demonstrated that many patients with anti-HCV core titer of 30 U or less are negative for HCV-RNA, and some of these are SVR patients who became HCV-RNA negative through previous IFN therapy. We also demonstrated a negative correlation between interval after IFN therapy and anti-HCV core titer in SVR patients.

We previously showed with short-term administration of IFN β over 8 consecutive weeks that a high proportion of patients with lower anti-HCV core titer at the end of therapy than at the start become SVR. Based on this finding, we observed serial changes in anti-HCV core titer during treatment with peginterferon, which is administered over a longer interval, in order to investigate whether it could be a predictive marker for ultimate therapeutic efficacy at an early stage following the start of therapy. We further investigated whether chasing changes in anti-HCV core titer make it possible to select more efficient peginterferon regimens suited to individual patients, and thus avoid side effects.

Anti-HCV core titer in SVR patients decreased continuously after the start of therapy and exhibited further decreases after the end of therapy in both the group taking peginterferon and ribavirin combination therapy, which is mostly administered for 48 weeks, and the group taking peginterferon monotherapy, which is mostly administered for 24 weeks. At the same time, in non-SVR patients, there was no clear decrease in anti-HCV core titer after the start of therapy, while there was an increase after the end of therapy. Looking at the changes in ALT levels, non-SVR patients had lower levels than SVR patients after the start of therapy, and conversely SVR patients showed significantly lower levels at the end of therapy. In addition, there were SVR patients whose ALT levels increased rather than decreased during therapy, and non-SVR patients who maintained normal levels during therapy. However, the SVR patients with increased ALT levels showed a continuous decrease in anti-HCV core titer.

It therefore appears that therapeutic efficacy cannot readily be predicted by changes in ALT levels during therapy, while observing changes in anti-HCV core titer is useful for predicting therapeutic efficacy. In addition, as 12 of 13 SVR patients were EVR, it appears that shortening the therapy period can be considered for both peginterferon and ribavirin combination therapy and peginterferon monotherapy when the patient is EVR and anti-HCV core titer decreases continuously during therapy. In fact, 2 of 3 patients in whom therapy was stopped due to side effects were SVR, and one of these was EVR.

HCV shows lymphotropism and is found in various tissues other than the liver, and it is thus likely that other infected tissues contribute to persistent infection and reactivation by acting as a reservoir for HCV. Immune complexes that accumulate in the blood circulation would also constantly trigger autoimmunity. HCV-infected patients are known to exhibit thyroid gland disorder and other extrahepatic manifestations, and the
occurrence of autoimmune disorders during interferon treatment is believed to be because interferon augments the characteristic background factors of HCV that are already present in the HCV-infected patient. Therefore, unnecessary continuous IFN administration should be avoided in order to prevent such side effects. It is likely that observing changes in anti-HCV core titer will make it possible to choose more appropriate peginterferon therapy methods and administration periods when using peginterferon to treat chronic hepatitis C in patients with a background that suggests risk.

References
2) Ishikawa K., Nitatori T. et al.: A case with hepatitis C who displayed hyperthyroidism followed by hypothyroidism during the course of peg-interferon monotherapy: relevance to changes in thyroid autoantibodies titer. Journal of the Faculty of Nursing, Iwate Prefectural University 12, 107-115, 2010
3) Ishikawa K.: Hepatitis C virus antibodies. KAN · TAN · SUI 43, 669-675, 2001
和文要旨
C型慢性肝炎例でpeginterferon治療（ribavirin併用例を含む）を受けた19例を対象とし、治療開始時から経時的にALT、HCV-RNA、anti-HCV core titerを測定した。anti-HCV core titerは、peginterferon・ribavirin併用療法群およびpeginterferon monotherapy療法群とも、SVR例では治療開始後から増加して減少し、治療終了時には減少率は50%に達し、治療終了後はさらに減少を示した。一方non SVR例では、治療開始後も減少傾向は明らかではなく、治療終了後は逆に増加を示した。またSVR例13例中12例がEVRであったことから、EVRで治療中anti-HCV core titerが持続減少を示す場合には、peginterferon・ribavirin併用療法例、peginterferon monotherapy療法例とも治療期間の短縮を考慮することが可能と考えられる。このことはリスク背景を有するC型慢性肝炎例に対する、不要な継続治療を避けより適切なpeginterferonの治療法および治療期間の選択に貢献するものである。

キーワード：C型肝炎、ペグインター・フィロン、リバビジョン、HCV コア抗体、副作用