Flares in chronic hepatitis B patients induced by the host or the virus? 
Relation to treatment response during Peg-interferon α-2b therapy

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Abbreviations: HBeAg, hepatitis e antigen; HBsAg, hepatitis B surface antigen; IFN, interferon; ALT, alanine transferase; HBV, hepatitis B virus; HBV DNA, hepatitis B virus deoxyribonucleic acid; Peg, pegylated; CHB, chronic hepatitis B; ULN, upper limits of normal; WBC, white blood cell count;

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Abstract
Background and aims: Flares are a well-known phenomenon during antiviral treatment for chronic hepatitis B. Little is known about the effect of flares on response. We investigated the timing and characteristics of flares, in relation to treatment response (HBeAg-loss).
Patients: 266 patients, participating in a global randomized controlled study were assigned to 52 weeks of 100µg Peg-interferon α-2b weekly combined with either daily 100mg lamivudine or placebo.
Results: Sixty-seven patients (25%) exhibited 75 flares, with 38(51%) flares in the combination-therapy and 37 (49%) in the mono-therapy group. Overall, 30% of patients with and 38% of patients without a flare responded to therapy (p=0.25). In 24 patients (36%) the flare was followed by a decrease of HBV-DNA (host-induced flare). In 25(38%) patients the flare was preceded by an increase of HBV-DNA (virus-induced flare). In 17(26%) patients the flare did not meet one of these criteria (indeterminate flare). Of patients with host-induced flare 58% responded, whereas only 20% of patients with virus-induced flares responded, p=0.008. HBsAg loss (n=8) was exclusively seen in patients experiencing a host-induced flare. Multivariate logistic analysis showed that host-induced flares was a independent predictor for response (p=0.043).
Conclusion: Flares are not more common in responders than in non-responders to Peg-interferon α-2b therapy. Virus-induced flares, which occur after an increase in HBV-DNA level, and most probably indicative for increased expression of viral antigens, did not lead to treatment response. In contrast, host-induced flares which were followed by an HBV-DNA decrease were highly associated with treatment response.
Introduction

Approximately 400 million people worldwide are chronically infected with the hepatitis B virus (HBV). Chronic infection with HBV can lead to progression of liver diseases with increased risk of cirrhosis, liver failure and hepatocellular carcinoma (1).

Currently, interferon-α (IFN), lamivudine and adefovir are the only registered drugs for treating chronic hepatitis B (CHB). During the treatment with IFN and after withdrawal of lamivudine therapy, flares of inflammatory activity are a well-known phenomenon in CHB patients. Flares can be life threatening, but have also been associated with virological response.

IFN-induced flares affect 25-40% of patients and have been attributed to the stimulatory effect of IFN, which is capable of increasing the T cell cytolytic activity and natural killer cell function. (2) Typically, these flares are thought to occur in HBeAg-positive patients during the second to third month of therapy, and may precede HBeAg seroconversion (2-5). In our previous observation flares during IFN were accompanied by an increased number of CD8+ specific T lymphocytes (6).

Lamivudine-related flares are seen during treatment, however they do not occur more often than in the natural course of CHB (3). More important appear the flares found after withdrawal of lamivudine, which occur in approximately 10-20% of patients (3, 7). These flares are probably caused by re-occurrence of HBV replication, and have been associated with decompensation of liver disease.

To clarify the role of flares during and after cessation of therapy, and to determine their relation with treatment response, we analyzed 266 HBeAg-positive CHB patients who received Peg-interferon α-2b alone or in combination with lamivudine.
Patients and Methods

Patients and Study design

The data were extracted from a global multicenter randomized controlled trial comparing Peg-interferon α-2b combined with either lamivudine or placebo in CHB (8). Patients were assigned in a 1:1 ratio to receive 100μg Peg-interferon α-2b weekly with 100mg lamivudine daily (combination-therapy) or 100μg Peg-interferon α-2b weekly with placebo (mono-therapy). Course of therapy was 52 weeks. After 32 weeks, the dose of Peg-interferon α-2b was halved to 50μg per week. Post-treatment follow-up lasted 26 weeks.

Patients were eligible for treatment if they were 16 years of age or older, had been positive for hepatitis B surface antigen (HBsAg) for at least six months, had been HBeAg positive on two occasion within 8 weeks prior to randomization and had two episodes of elevated serum ALT levels (at least 2 times the upper limit of normal (ULN)) on two occasions within 8 weeks prior to randomization.

Patients were excluded for the following reasons: treatment with antiviral medication within 6 months or any investigational drug within 30 days of entry to the protocol, presence of serum antibodies against hepatitis C virus, hepatitis D virus or human immunodeficiency virus. Other exclusion criteria were: alcoholic hepatitis or other causes of liver disease; pre-existing leukopenia (white blood cell count (WBC) ≤ 3,000/mm³), thrombocytopenia (platelets ≤ 100,000/mm³) or granulocytopenia (granulocytes ≤ 1,800/mm³); decompensated liver disease (prothrombin time prolonged by ≥ 3 sec, serum albumin < 35 g/l, ascites, encephalopathy, history of variceal bleeding) or hypo- or hyperthyroidism. Patients were also excluded in the event of any contraindication specified for IFN. The Ethics committee at the participating centers approved the protocol, and all patients provided written informed consent.

Monitoring

All patients were seen monthly during therapy and follow-up. At each visit, patients attended the outpatient clinic for ALT measurement and other laboratory assessments. Transaminases were assessed locally and therefore expressed as times the ULN. Corresponding to Honkoop et al. (7), a flare was defined as a 3-fold increase of serum ALT compared to baseline level. The time point of flare was defined as the time of the peak level of serum ALT. Multiple peak levels of thrice baseline serum ALT level were considered as different flares, if they were separated by at least 2 measurements of ALT. In addition to ALT, HBV DNA (detection limit 400 copies/ml, using in-house Taqman PCR based on the Eurohep standard (9)) was assessed at the same time points. Other virological parameters, such as HBeAg (AxSYM, Abbott, Chicago, Ill) and HBsAg (AxSYM, Abbott, Chigaco, Ill) were assessed at baseline, at week 32, 52 (end of treatment) and 78 (end of follow-up). HBV genotype was assessed by Inno-Lipa assay (Innogenetics, Gent, Belgium). Response to therapy was defined as serum HBeAg loss at the end of follow-up.

Statistical analysis

Chi-square or Fisher’s exact test was used for categorical variables, and Mann-Whitney U test was performed for continuous data. In order to determine independent predictors for the event flare, the baseline characteristics age, race, sex, mode of transmission, pre-existing cirrhosis, ALT, log HBV DNA, HBV genotype and previous IFN, were included in the univariate analysis. All tested variables with a p-value < 0.15 were
entered in the multivariate time-dependent Cox-regression analysis. In order to determine independent predictors for response within the flare population, we included the above mentioned baseline variables plus timing of flare, peak value of ALT during exacerbation, and flare type (host-induced vs. virus-induced) in a univariate and multivariate analysis. In the event of multiple flares the first flare was analyzed for response to therapy. All data were analyzed using SPSS (version 10.1 SPSS Inc., Chicago, IL). A p-value of 0.05 was considered significant (all two-tailed).
Results

Flare versus non-flare

Among the 266 patients analyzed, 75 flares were recorded in 67 (25%) patients. Six patients experienced 2 flares and 1 patient 3 flares during treatment or follow-up. The median time point of flare was at week 60 (range 4 to 78), and median peak of ALT during flares was 12.3 x ULN (range 2.3 to 60.0). Of the 75 flares, 35 (47%) occurred during treatment and 40 (53%) after treatment discontinuation. In 3 patients, of whom 2 had pre-existing cirrhosis, the flare was reported as a serious adverse event (SAE); in 1 of them this led to early cessation of treatment. One patient had signs of diminished liver function (bilirubin 62 µmol/L) during the flare episode, which resolved after normalization of ALT values. During the flare there were no other signs of hepatic decompensation.

Characteristics of patients with and without flare are given in table 1.

Table 1. Characteristics at baseline of 266 patients with or without a flare of chronic hepatitis B patients.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Flare N = 67</th>
<th>No Flare N = 199</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>34±12</td>
<td>35±13</td>
<td>0.804</td>
</tr>
<tr>
<td>ALT* (x ULN)</td>
<td>2.9±1.4</td>
<td>4.8±3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log HBV DNA*</td>
<td>9.1±1.1</td>
<td>9.1±0.9</td>
<td>0.764</td>
</tr>
<tr>
<td>Male (%)</td>
<td>52(78)</td>
<td>153(77)</td>
<td>0.947</td>
</tr>
<tr>
<td>Transmission (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- vertical</td>
<td>18(27)</td>
<td>42(21)</td>
<td>0.132</td>
</tr>
<tr>
<td>- (homo)sexual</td>
<td>7(10)</td>
<td>22(11)</td>
<td></td>
</tr>
<tr>
<td>- parenteral</td>
<td>8(12)</td>
<td>21(11)</td>
<td></td>
</tr>
<tr>
<td>- transfusion</td>
<td>4(6)</td>
<td>3(2)</td>
<td></td>
</tr>
<tr>
<td>- unknown</td>
<td>30(45)</td>
<td>111(56)</td>
<td></td>
</tr>
<tr>
<td>Genotype (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- A</td>
<td>19(28)</td>
<td>71(36)</td>
<td>0.738</td>
</tr>
<tr>
<td>- B</td>
<td>7(10)</td>
<td>16(8)</td>
<td></td>
</tr>
<tr>
<td>- C</td>
<td>11(16)</td>
<td>28(14)</td>
<td></td>
</tr>
<tr>
<td>- D</td>
<td>26(39)</td>
<td>77(39)</td>
<td></td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Caucasian</td>
<td>47(70)</td>
<td>149(75)</td>
<td>0.432</td>
</tr>
<tr>
<td>- Asian</td>
<td>13(19)</td>
<td>39(20)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis (%)</td>
<td>10(19)</td>
<td>14(7)</td>
<td>0.060</td>
</tr>
<tr>
<td>Previous lamivudine (%)</td>
<td>8(12)</td>
<td>31(16)</td>
<td>0.459</td>
</tr>
<tr>
<td>Previous Interferon (%)</td>
<td>12(18)</td>
<td>47(24)</td>
<td>0.311</td>
</tr>
<tr>
<td>Mono-therapy (%)</td>
<td>32(48)</td>
<td>104(52)</td>
<td>0.566</td>
</tr>
<tr>
<td>Combination therapy (%)</td>
<td>35(52)</td>
<td>95(48)</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± SD
Except for ALT and cirrhosis, all variables at baseline were comparable in the flare and the non-flare group. Ten patients (19%) in the flare group and 14 (9%) patients in the non-flare group had pre-existing cirrhosis (p = 0.06). Pre-existing cirrhosis (p = 0.046; relative risk 2.0 95% CI 1.0 to 4.0) and lower ALT at baseline (p < 0.0001 relative risk 1.4 95% CI 1.2 to 1.6) were also the only two independent predictors for experiencing a flare during therapy or follow-up.

Among the 75 flares, we recorded 37 (49%) in the mono-therapy group (35 patients) and 38 (51%) the combination therapy group (32 patients). Baseline characteristics and response to therapy were not significantly different between patients with a flare undergoing mono-therapy or combination therapy (table 2). In 5 patients who exhibited a flare during or after treatment with combination of Peg-interferon α-2b and lamivudine a YMDD mutant was detected. None of the flares were related with the emergence of a YMDD mutant.

Table 2. Characteristics of patients who had a flare according to therapy

<table>
<thead>
<tr>
<th></th>
<th>PEG-IFN Placebo N = 32 (48%)</th>
<th>PEG-IFN Lamivudine N = 35 (52%)</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>36 ± 13.1</td>
<td>33 ± 10.8</td>
<td>0.44</td>
</tr>
<tr>
<td>Male (%)</td>
<td>24 (75)</td>
<td>28 (80)</td>
<td>0.77</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Caucasian</td>
<td>21 (66)</td>
<td>26 (74)</td>
<td></td>
</tr>
<tr>
<td>Asian/Mongoloid</td>
<td>7 (22)</td>
<td>6 (17)</td>
<td></td>
</tr>
<tr>
<td>ALT* (x ULN)</td>
<td>2.9 ± 1.3</td>
<td>2.9 ± 1.5</td>
<td>0.94</td>
</tr>
<tr>
<td>Log HBV DNA*</td>
<td>8.9 ± 1.3</td>
<td>9.2 ± 0.9</td>
<td>0.25</td>
</tr>
<tr>
<td>Genotype (%)</td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>A</td>
<td>9 (28)</td>
<td>10 (29)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>2 (6)</td>
<td>5 (14)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>7 (22)</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>11 (34)</td>
<td>15 (43)</td>
<td></td>
</tr>
<tr>
<td>Pre-existing Cirrhosis (%)</td>
<td>5 (16)</td>
<td>5 (14)</td>
<td>0.99</td>
</tr>
<tr>
<td>Dose reduction (%)</td>
<td>11 (34)</td>
<td>13 (37)</td>
<td>0.81</td>
</tr>
<tr>
<td>Discontinuation of treatment (%)</td>
<td>4 (13)</td>
<td>5 (14)</td>
<td>0.83</td>
</tr>
<tr>
<td>Flares during treatment (%)</td>
<td>20 (63)</td>
<td>14 (40)</td>
<td>0.067</td>
</tr>
<tr>
<td>Time of flare †</td>
<td>36 (4-78)</td>
<td>60 (4-78)</td>
<td>0.27</td>
</tr>
<tr>
<td>peak value flare* (x ULN)</td>
<td>13.7±6.9</td>
<td>16.4±13.8</td>
<td>0.89</td>
</tr>
<tr>
<td>Response (%)</td>
<td>10 (31)</td>
<td>10 (29)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

* Mean ± Sd
† Median (range)
Flares in relation to response to treatment and genotype

Among the 67 flare patients, 20 (30%) responded to therapy, 10 (31%) in the mono-therapy and 10 (29%) in the combination group. Eight patients (12%) exhibited loss of HBsAg at end of follow-up. On-treatment flares led more often to treatment response (41%) than post-treatment flares (21%), (p = 0.081, figure 1).

The frequency of flares was comparable for patients with different HBV genotype (figure 2A). However, the timing of flares and response to therapy differed among the HBV genotype. A total of 17 (74%) flares were recorded on-treatment in patients harboring genotype A, versus 3 (43%) in genotype B, 4 (33%) in genotype C, and 8 (27%) in genotype D (genotype A versus other genotypes P = 0.046; figure 2B). Treatment response in the flare population was 47% for genotype A, 28% for B, 18% for C, and 19% for D (genotype A versus genotype D, p = 0.05, figure 2C). In addition to timing of flares and HBV genotype, the magnitude of ALT elevation was associated to treatment response Mean ALT during flare within responders was 20.1 x ULN versus 13.2 x ULN in non-responders, (p = 0.036).

Host-induced versus virus-induced flares

Close on-line monitoring of the serum ALT and the HBV DNA levels revealed different patterns of exacerbations (figure 3). A flare was defined as ‘virus-induced’ when preceded by an increase of least 1 log HBV DNA within 4 months. In general, these flares did not lead to a decline serum HBV DNA. A flare was defined as ‘host-induced’ when preceding HBV DNA levels were stable and when the flare was followed by a decline of 1 log HBV DNA or more within the 4 months thereafter. Flares that did not meet one of these criteria were classified as indeterminate. Only the first occurring flares were classified. For both host- and virus-induced flares a minimum of 1 log HBV DNA alternation was chosen to exclude random oscillation of serum HBV DNA as a basis for our flare criteria.

Twenty-four flares (36%) were characterized as host-induced, 25 (38%) were virus-induced, and 17 (26%) were indeterminate. One flare could not be classified due to missing HBV DNA levels. Among the 67 flare patients, a host-induced flare was strongly related to response to therapy (figure 4). Fourteen of the 24 patients (58%) with a host-induced flare responded to therapy, as compared to five of the 25 patients (20%) with a virus-induced, and one patient (6%) with an indeterminate flare. Moreover, 8 patients (33%) with a host-induced flare, but none of those with a virus-induced or indeterminate flare were HBsAg negative at the end of follow-up. Seventy-five percent of the host-induced flares versus 16% of the virus-induced occurred during treatment, (p < 0.0001). Median peak of ALT of host induced-flares was 13.8 x ULN (range 5.3 to 60) and 12.1 x ULN (range 3 to 45) for virus-induced flares. Eleven patients (61%) with a host-induced flare during treatment, and 3 (50%) with a host-induced flare after treatment responded to therapy. One patient (25%) with a virus-induced flare during treatment and 4 (19%) with a virus-induced flare after treatment responded to therapy. Within the flare population multivariate analysis showed that the occurrence of host-induced flare (p = 0.043, RR 3.5 CI 0.9 to 13.9) and the magnitude of ALT elevation (p = 0.031 RR 1.1 95% CI 1.0 to 1.1) were the only factors independently predictive for response (serum HBeAg loss). On-treatment flares were not significant related to response in this analysis (p = 0.65, RR 1.4 95%CI 0.3 to 6.7).

After entering the occurrence of host-induced flares the previously described multivariate analysis (8) of the total study population (n=266), it remained a significant variable predicting response. (RR 2.4, CI 1.0 to 5.8, p = 0.05)
Discussion

Spontaneous or treatment-induced flares of inflammation are frequently observed in CHB. These abrupt elevations in serum ALT are the result of an increase of intrahepatic necroinflammation associated with expanded numbers of intrahepatic lymphocytes, in particular cytotoxic T lymphocytes. Cytotoxic T lymphocytes are important to control HBV, but can also induce liver damage, depending on the environment and functional capability (10-15). Therapy with IFN is based on its stimulating effect on the cytotoxic T lymphocyte and natural killer cell function. Flares during standard IFN treatment occur typically during the second and third month, and are thought to the herald virological response and disease remission (2-5, 16). Probably, these flares represent an attempt of the immune system to clear the HBV infection.

In the current study, 29 percent of the patients experienced a flare during therapy (n=34) or follow-up (n=33). We did not find a significant difference between the number of flares in patients treated with Peg-interferon α-2b alone versus those treated with Peg-interferon α-2b in combination with lamivudine. Patients with low baseline ALT or pre-existing cirrhosis were more prone to have flares. Cirrhotics tended to experience flares with high ALT values. These patients should be monitored carefully during treatment with Peg-interferon α-2b, not only because of their increased risk of flares but also because of their diminished residual liver function and the consequent risk to develop decompensated liver disease. In the current study no permanent or life-threatening signs of liver failure were encountered.

Overall, flares were not associated with response to therapy. However, flares during treatment were more often associated with response than flares after treatment (figure 1). In addition to the timing of flares, response was dependent of HBV genotype and the magnitude of the flare. Previously, a strong association between the severity of flares and HBsAg seroconversion has been found both in the natural history of CHB, and in the setting of IFN therapy (16, 17). In these studies different definitions of flares have been used. Nair et al. defined a flare as an increase of ALT at least twice the ULN compared to baseline values while Yuen et al. defined flare as elevated transaminases above twice the ULN. Since our patients had already high baseline serum ALT levels (ALT levels above twice the ULN was used as an entry criterion in this study population), these definitions were less suitable. For a clear distinction between flares and relative mild elevations of serum ALT, we based our definition on our previous experience. in which a 3-fold increase of serum ALT from baseline was used (7).

An important finding of the current study are the distinct patterns of flares occurring with stable viral load followed by a viral load decrease (host-induced flares) versus flares preceded by an increase of viral load, and variable viral loads afterwards (virus-induced flares). The patients with host-induced flares responded significantly better to therapy than those with a virus-induced flare. Multivariate analysis revealed host-induced flare as the only independent factor predicting treatment response. Interestingly, all patients undergoing HBsAg seroconversion had a host-induced flare. This further supports the hypothesis that full control and elimination of the virus, as indicated by clearance of HBeAg and HBsAg, is achieved by a vigorous host immune response rather than by direct suppression of the virus. Previous studies have shown that both spontaneous or interferon-α induced exacerbations of hepatocellular necrosis in CHB are associated with an induction of a virus-specific CD4+ T cell response (18, 19). Under interferon-α therapy such a hepatitis flare preceding sustained HBeAg seroconversion, requires a substantial increase in IL-12 production, along with the induction of the Th1 cytokines IFN-α and IL-2 (20).

Virus-induced flares, which emerged after increasing levels of HBV DNA, were related to treatment with the combination with lamivudine, and more frequently seen after therapy.
These flares could be attributed to the reactivation of HBV after withdrawal of lamivudine. In general they do not lead to disease remission, but have been associated with clinical exacerbations and disease progression (7) In our study, virus-induced flares did usually not lead to response, and even appeared to be detrimental rather than beneficial for treatment response. Virus-induced flares are not restricted to CHB patients treated with IFN and or lamivudine, but also occur during the natural history of the disease. Liu et al. described several patients in whom significant flares were preceded by an increase of HBV DNA (21). Studies in anti-HBe positive patients showed also episodes of flares as a result of sudden reactivation of HBV (22-24).

In general, flares during treatment with IFN or Peg-IFN should not be treated with nucleoside analogues, and IFN should only be discontinued in case of impending liver failure. Particular care should be taken in patients with cirrhosis who are at highest risk of developing liver failure. On-treatment flares are likely to be a host- or IFN-induced flares, and could well herald loss of HBeAg or even HBsAg. In contrast, flares after treatment, especially after lamivudine are in general the detrimental flares. These flares are typically seen after an increase of HBV DNA and seldom lead to treatment response. Retreatment with a nucleoside analogue should then be considered.

In conclusion, flares play an important role in the treatment with Peg-interferon α-2b alone or in combination with lamivudine, and patients with pre-existing cirrhosis are at greater risk for experiencing a flare. Furthermore, host-induced flares but not virus-induced flares may herald a response to therapy. It remains to be investigated, also for optimization of treatment, which virological and immunological mechanisms induce the specific flare patterns described in our study.
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Appendix

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Legend to figures

Figure 1. Proportion of response in relation to time point of flare. Early presence of flare increases chance of response, $p = 0.081$. Probability of response is shown on the Y-axis.

Figure 2. Figure 2A) Frequency of flares according to HBV genotype. Between the most important genotypes in our study, HBV genotype A, B, C and D ($n = 255$), no significant difference in frequency of flares was found. B) Proportion of flares recorded during treatment among the flare population according to HBV genotype ($n = 63$). On-treatment flares predominantly occurred within genotype A. Genotype A versus other genotypes D, $p = 0.029$ C) Flares leading to response according to genotype ($n = 63$). *genotype A versus genotype D, $p = 0.050$.

Figure 3. A) Case with host-induced flare: The elevation in serum ALT is followed by a decrease in viral load (log HBV DNA). Case with virus-induced flare (B): The serum ALT elevation is preceded by a sharp increase serum of HBV DNA.

Figure 4. Host-induced, indeterminate and virus-induced flares in relation to treatment response. Host-induced versus virus-induced, $p = 0.008$. 
References


A Host-induced flare

![Graph showing ALT and HBV DNA levels over time during treatment.](http://gut.bmj.com/)

- **ALT (x ULN)**
- **Log HBV DNA**
Figure 4

Treatment Response (%)

- Host-induced (N = 24): 58%
- Indeterminate (N = 17): 6%
- Virus-induced (N = 25): 20%
Flares in chronic hepatitis B patients induced by the host or the virus? Relation to treatment response during Peg-interferon α-2b therapy

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