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Prediction models for feverishness developed during interferon therapy of chronic hepatitis C patients

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Received July 7, 2009, accepted August 7, 2009

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Pharmazie 65: 114–116 (2010) *doi: 10.1691/ph.2010.9698*

Pegylated interferon (peginterferon) and ribavirin combination therapy is used extensively for therapy of chronic hepatitis C. Most patients that receive this therapy are known to develop influenza-like symptoms with fever and headache. Therefore, we attempted to construct a multiple-regression model to predict the intensity of feverishness from the profiles of such patients. A retrospective survey of the medical charts of patients with chronic hepatitis C that have been on peginterferon-α-2b and ribavirin combination therapy was performed. Body temperatures of patients at 8.5 h after receiving interferon injection on day one of therapy were the objective variables. Patients' profiles such as sex, age, and blood test results before the injection were defined as explanatory variables. Genetic algorism with leave-one-out cross-validation as selection pressure was applied in the selection of variables. The final model for prediction was determined by bootstrap validation. As a result, a significant multiple-regression model including sex, BUN, and leukocyte count as descriptors was constructed. The prediction of patients with severe fever in the model equation is of some help regarding the proper use of antipyretics in interferon therapy.

1. Introduction

Pegylated interferon (peginterferon, PEG-IFN) was recently developed (Bukowski et al. 2002). To date, PEG-IFN and ribavirin combination therapy has been commonly-applied as a definitive therapy of chronic hepatitis C (NIH 2009). On the other hand, some of adverse effects appeared in therapy of PEG-IFN. In the Japanese Ethical Drug Package Insert for PEG-IFNα-2b (Schering-Plough Corporation 2007), the incidences of influenza-like symptoms such as feverishness, malaise, and headache were 95.5%, 93.4%, and 88.6%, respectively. In particular, these symptoms are frequently developed in the initial therapy (NIH 2009), and may hamper a successful outcome of the therapy. Recently, we reported the relationship between the degree of seriousness of feverishness in the PEG-IFN therapy and patients' profiles (Motegi et al. 2008). Female patients have a greater tendency to develop severe fever, more specifically, higher peak body temperatures and longer sustained term of anomalous body temperatures than males. Furthermore, tendency of feverishness was classified into two groups based on the time to reach maximum body temperature. The early and slow fever-developing groups reached maximum body temperature within and after 12 hours post administration, respectively. The early group had significantly higher maximum body temperatures, more persistent fever, and a higher female ratio than the slow group. Maximal difference in body temperature between male and female, and the early and slow groups was found at 19:00 o'clock (8.5 h after PEG-IFN administration) on the first day of the PEG-IFN therapy. In the present study, construction of a static regression model to predict body temperature in the PEG-IFN therapy for each patient based on their background was attempted using profiles of hospital patients that received PEG-IFN-ribavirin combination therapy for chronic hepatitis C.

2. Invertigatious and results

Thirty-six patients (18 males and 18 females) in the consultation period were surveyed in the study. The ages ranged from 30 to 67 years (average 53.5 years). Maximum body temperature was $38.1 \pm 0.7\,^{\circ}C$ (mean and SD). Patients that did not use the antipyretics until 19:00 p.m. of the first day were excluded from all the analyses. Thus, 28 patients (13 males and 15 females) were analyzed. The ages ranged from 30 to 67 years (average 53.8 years), and maximum body temperature was $38.2 \pm 0.5\,^{\circ}C$ (mean ± SD). Prediction model equation for body temperature was investigated with the temperature at 19:00 p.m. as the objective variable. As a result, 5 significant linear regression models were selected by genetic algorism with sex, BUN (mg/dL), WBC ($\times 10^3/\mu L$, BW (kg), and AST (IU/L) as the variables.

$$\begin{aligned} BT = {} & 0.465\ (\pm 0.266)\ \text{Female} + 0.213\ (\pm 0.009)\ WBC \\ & - 0.548\ (\pm 0.292)\ BUN + 0.0222\ (\pm 0.0102)\ BUN^2 \\ & - 0.0173\ (\pm 0.0126)\ BW + 40.6 \end{aligned} \quad (1)$$

($n = 28$, $R^2 = 0.561$, Q^2 (loo) $= 0.330$, Q^2 (bootstrap) $= 0.223$, $F = 5.63$, $s = 0.554$, $p = 0.0017$)

$$\begin{aligned} BT = {} & 0.620\ (\pm 0.246)\ \text{Female} + 0.140\ (\pm 0.081)\ WBC \\ & - 0.579\ (\pm 0.296)\ BUN + 0.0233\ (\pm 0.0104)\ BUN^2 \\ & + 40.0 \end{aligned} \quad (2)$$

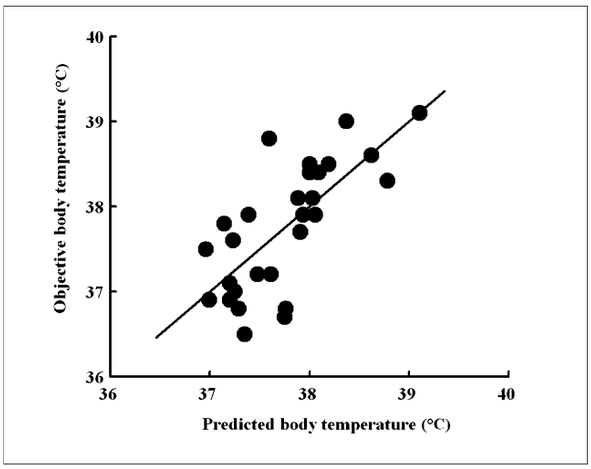

Fig. 1: Scatter plots between predicted and observed body temperatures at 19:00 p.m. on the first day of peginterferon therapy. The final regression model (equation 2) was used in the calculation

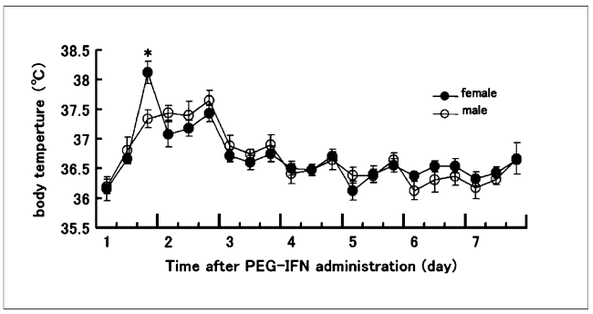

Fig. 2: Changes in body temperature after peginterferon administration in male and female groups. Each point and vertical bar represents the mean and S.E. (14 males and 14 females). Body temperature data were acquired from not including antipyretic treatment. *$p < 0.05$ compared with the values in the male patients. (This figure was cited from the literature (Motegi et al. 2008))

($n = 28$, $R^2 = 0.524$, Q^2 (loo) $= 0.328$, Q^2 (bootstrap) $= 0.270$, $F = 6.32$, $s = 0.565$, $p = 0.0014$)

$$BT = 0.255\ (\pm 0.097)\ WBC - 0.746\ (\pm 0.280)\ BUN + 0.0291 (\pm 0.0099)\ BUN^2 - 0.0266\ (\pm 0.0119)\ BW + 42.5 \quad (3)$$

($n = 28$, $R^2 = 0.500$, Q^2 (loo) $= 0.326$, Q^2 (bootstrap) $= 0.240$, $F = 5.67$, $s = 0.578$, $p = 0.0023$)

$$BT = 0.602\ (\pm 0.265)\ Female + 0.146\ (\pm 0.085)\ WBC - 0.612\ (\pm 0.342)\ BUN + 0.0245\ (\pm 0.0122)\ BUN^2 - 0.116\ (\pm 0.553)\ \log AST + 40.4 \quad (4)$$

($n = 28$, $R^2 = 0.525$, Q^2 (loo) $= 0.307$, Q^2 (bootstrap) $= 0.182$, $F = 4.86$, $s = 0.577$, $p = 0.0038$)

$$BT = 0.459\ (\pm 0.282)\ Female + 0.215\ (\pm 0.099)\ WBC - 0.562 (\pm 0.338)\ BUN + 0.0227\ (\pm 0.0121)\ BUN^2 - 0.0172\ (\pm 0.0129)\ BW - 0.0172 (\pm 0.546) \log AST + 40.0 \quad (5)$$

($n = 28$, $R^2 = 0.561$, Q^2 (loo) $= 0.304$, Q^2 (bootstrap) $= 0.119$, $F = 4.48$, $s = 0.567$, $p = 0.0045$)

If the patient is female then "female" = 1, if male then "female" = 0. "BT" indicates body temperature after 8.5 h from the first PEG-IFN administration.
Fig. 1 shows a scatter plot of predicted body temperatures in Eq. (2) against the maximal Q^2 (bootstrap) and objective body temperatures.

3. Discussion

Sex difference was noted in the tendency of feverishness during the PEG-IFN therapy in the previous study (Motegi et al. 2008) on the same patients that were included in this study. That is, the times to reach maximum body temperatures were significantly shorter in the female patients than in the male patients (female, 14.4 min; male 20.9 min). On the other hand, body temperatures just before administration of the on-demand antipyretics were maximal for all the patients that used the antipyretics. Therefore, patients that did not use the antipyretics until 19:00 p.m. of the first day were excluded in order to eliminate other drug effects in the characterization of feverishness with PEG-IFN.

Fig. 2 shows the time-course of the average body temperature of the male and female patients after administration of PEG-IFN (Motegi et al. 2008). The average body temperature at 19:00 o'clock, 8.5 h after the initial PEG-INF administration on the first day of treatment was the maximum (37.8 ± 0.8 °C). At this time, the average body temperature of the female patients was higher than that of the male patients (male, 37.3 ± 0.6 °C; female, 38.1 ± 0.7 °C). Body temperatures at the time point was considered suitable to represent the tendency of feverishness with PEG-IFN because body temperature is able to distinguish the characteristics of female patients from males in that they are more sensitive towards feverishness. Furthermore, the early and slow groups were also distinguished at this point. Therefore, prediction model equation for this body temperature at the point was studied. Top 5 linear regression models for Q^2 (loo) included female, BUN, WBC, BW, and AST as the explanatory valuables. As a result of a bootstrap validation, Eq. (2) was selected as the final model with the most predictive performance in the models. The "female" variable was introduced as a dummy variable during the selection of variables by genetic algorithm. The positive partial regression coefficient of "female" correlated well with the result that female patients were more sensitive than male patients for body temperatures at 19:00. "WBC" was also introduced for the selection of variables. It has been reported that frequency of WBC decline is high in side effects during PEG-IFN therapy (Balan 2005; Schering-Plough Corporation 2007). This knowledge suggests that the sensitivity of the feverishness of patient in IFN therapy might be related with the leukocyte count. In addition, "BUN" and "squared BUN" were incorporated into the final equation. The relationship between BUN and body temperature was fitted significantly with a quadratic function of BUN ($r = 0.571$, $p = 0.007$). This relational expression showed that the lowest body temperature can be estimated in patients with 13 mg/dL of BUN. High and low BUN values indicate aberrance of renal and liver functions, respectively (Lyman 1986; Magarian 1992; Inoue 2005). The relationship between body temperatures and BUN might reflect renal and hepatic clearance of PEG-IFN. In the case categorized in the early and slow fever-developing groups, maximum body temperature was reached within and after 12 h of the administration, Ccr values in the early group were significantly lower than those in the slow group (early, 90.3 ml/min; slow, 118.5 ml/min) (Motegi et al. 2008). This finding suggests a relationship between renal function and feverishness with IFN because patients in the early group experienced more serious fever (higher maximum body temperatures and longer duration of fever) than those in the slow group. On the other hand, the liver is the main catabolic site of IFN as is the kidney. (Satoh et al. 1984). That is, sensitivities of the adverse effect might be increased in the patients with hepatic

impairment. It is considered that BUN and the square values were introduced into the final model as a parameter related to effects of both renal and hepatic functions.

We succeeded in constructing a significant model for the prediction of feverish with rational patients' background as the explanatory variables. The findings in the present study might prove helpful for proper use of antipyretics in PEG-IFN therapy.

4. Experimental

This study was approved by the Ethics Committee in Saitama Social Insurance Hospital.

4.1. Data acquisition

A retrospective study of medical records from February 2005 to August 2007 in Saitama Social Insurance Hospital was performed for the hospital patients that received the first PEG-IFNα-2b and ribavirin combination therapy for chronic hepatitis C. Patients that received antipyretics together with the initial dosing of PEG-IFN were excluded from survey. Consultation period was established as the day of the initial PEG-IFN injection. Patients that injected PEG-IFN between 10:00 a.m. and 11:00 a.m. were analyzed, so administration of the injection time was set at 10:30 a.m. in this study. Diclofenac suppositories were prescribed as antipyretics for the patients who asked to use them. Body temperature, adjacent injection of PEG-INF, sex, age, body weight, amount of viral RNA, genotype of hepatitis C virus, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), serum creatinine level (Cr), predicted creatinine clearance (Ccr), amount of PEG-INF and ribavirin, leukocyte count (WBC), platelet count, and hemoglobin level were used in the analysis to predict the body temperature after 8.5 h of PEG-INF injection.

4.2. Data analysis

The relation between body temperatures after 8.5 h from the initial injection of PEG-INF and a variety of parameters from the patients' backgrounds was investigated using statistical techniques including multi-regression analysis with variable subset selection-genetic algorithm (VSS-GA) (Leardi 1992) with leave-one-out cross-validation (Tetko 2001) as selection pressure by MobyDigs software version 1.0 (Talete srl, Pisani, Milano, Italy). In the genetic algorithm, maximal number of the explanatory variables mounted in the constructing multiple-regression equations was limited to 6 for the equations to remain flexible. The final model was selected as the best equation to determine coefficients of the bootstrap-validation (Q^2 bootstrap) (Efron 1987) from the top 5 equations out of 50 where coefficients are determined in the leave-one-out validation (Q^2 loo). Furthermore, the final model was validated by regression diagnostics using a normal residual plot and significant result of analysis of variance (ANOVA) by JMP version 8.0.1 (SAS Institute Inc., Cary, NC, U.S.A.).

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