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Temperature rise after peginterferon alfa-2a injection in patients with chronic hepatitis C is associated with virological response and is modulated by *IL28B* genotype

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Abstract

Background & Aims—Interferon treatment for chronic hepatitis C is associated with non-specific symptoms including fever. We aimed to determine the association of temperature changes with interferon antiviral activity.

Methods—60 treatment-naïve patients with chronic hepatitis C (67% genotype 1/4/6, 33% genotype 2/3) were admitted to start peginterferon alfa-2a and ribavirin in a clinical trial. Temperature was measured at baseline and 3 times daily for the first 24 h and the maximal increase from baseline during that time ($\Delta T_{\max}$) was determined. Serum HCV-RNA, interferon-gamma-inducible protein-10 (IP-10) and expression of interferon-stimulated genes (ISGs – *CD274*, *ISG15*, *RSAD2*, *IRF7*, *CXCL10*) in peripheral blood mononuclear cells (PBMCs) were measured at very early time points, and response kinetics calculated. The *IL28B* single nucleotide polymorphism, rs12979860, was genotyped.

Results—Temperatures rose by 1.2 ± 0.8 °C, peaking after 12.5 h. $\Delta T_{\max}$ was strongly associated with 1st phase virological decline ($r = 0.59$, $p < 0.0001$) and was independent of gender, cirrhosis, viral genotype or baseline HCV-RNA. The association with 1st phase decline was seen in patients with rs12989760CC genotype ($r = 0.65$, $p < 0.0001$) but not in CC/CT ($r = 0.13$, $p = 0.53$) and patients with CC genotype had a higher $\Delta T_{\max}$ (1.4 ± 0.8 °C vs. 0.8 ± 0.6 °C, $p = 0.001$). $\Delta T_{\max}$ was associated with 6- and 24-h induction of serum IP-10 and of PBMC ISG expression, but only in patients with rs12989760CC. $\Delta T_{\max}$ weakly predicted early virological response (AUC = 0.68, CI 0.49–0.88).

Conclusions—Temperature rise following peginterferon injection is closely associated with virological response and is modulated by *IL28B* polymorphism, reflecting host interferon-responsiveness. Published by Elsevier B.V. on behalf of the European Association for the Study of the Liver.

Keywords

Fever; Temperature; Interferon alfa; *IL28B*; Hepatitis C; Treatment

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jhep.2013.07.004>.

Introduction

Interferon (IFN) alpha, and in the past decade, pegylated interferon (PegIFN), have been the backbone of antiviral therapy for patients with chronic hepatitis C [1]. Treatment with PegIFN is commonly associated with side effects and especially influenza-like symptoms of pyrexia, myalgia, and rigors [2–4]. Several hours after a PegIFN injection, a rapid rise in body temperature is commonly noted, thought to be mediated by IFN activity on the hypothalamus and initiation of the febrile pathway. However, the factors that predict the magnitude of this febrile response and its association with the antiviral efficacy of PegIFN are yet unknown.

We hypothesized that the spike of fever after the initial PegIFN injection will reflect interferon responsiveness and be correlated with the antiviral efficacy, as determined by the first phase virological decline [5] and sought to determine which baseline and on-treatment factors affect it.

Materials and methods

Study design and population

A retrospective analysis of data from a prospective treatment trial [6]. Sixty treatment-naïve adult patients with chronic HCV infection were admitted as inpatients to the NIH Clinical Center for 5–6 days to undergo a liver biopsy and begin combination therapy with PegIFNalpha-2a and ribavirin (RBV) using standard doses and duration. All patients received their first PegIFN injection at 8:00 AM. Patients were allowed a single dose of acetaminophen (up to 650 mg) if needed for fever or pain. The study protocol was approved by the Institutional Review Board and all patients gave written informed consent (ClinicalTrials.gov registration NCT00718172).

Oral temperatures

Temperatures were measured by Kendall's Genius 2, an infrared tympanic electronic thermometer (Mansfield, MA) set in oral mode prior to the first injection of PegIFN, and once per 8 h shift for the first 24 h. Maximum oral temperature change ($\Delta T_{\max}$) was defined as the difference between the baseline temperature and the maximal recorded temperature within the first 24 h.

Viral kinetics

Quantitative HCV RNA levels were measured at baseline, 6, 24, 48, 72 h, and weekly from week 1 until week 4, and every 4–8 weeks thereafter, using Cobas TaqMan real-time polymerase chain reaction (Roche Diagnostics, Palo Alto, CA), with a lower limit of detection of 15 IU/ml. The first-phase virological decline was defined as the logarithmic decline in serum HCV RNA levels from baseline to the nadir of the first 72 h. The second-phase slope was defined as the log-linear slope of decline from week 1 to week 4, or to the last quantifiable measurement.

A fast response was defined as $\geq 2 \log_{10}$ drop in HCV RNA levels by week 4. Rapid virological response (RVR) was defined as undetectable virus at week 4. Patients who were HCV RNA negative or had a $\geq 2 \log_{10}$ drop in HCV RNA by week 12 were categorized as having a complete or partial early virological response (EVR), respectively. Patients who remained HCV RNA negative 6 months after stopping treatment were determined to have a sustained virological response (SVR).

Cytokine measurements

Serum levels of interferon-gamma-inducible-protein-10 (IP10), a serum protein which is the product of *CXCL10*, an interferon-stimulated gene (ISG), were measured by cytometric bead array (BD Biosciences, San Jose, CA) in a subset of 39 patients with samples drawn at baseline, 6 h, 24 h, 1, 2, 7, and 28 days after the first dose of PegIFN. Peripheral blood mononuclear cells (PBMCs) were obtained at the same time points and expression levels of *CXCL10*, *CD274*, *ISG15*, *RSAD2*, and *IRF7* were measured by quantitative PCR.

Genotyping

The *IL28B* single nucleotide polymorphism (SNP), rs12979860, was genotyped using TaqMan assay (Applied Biosystems Inc., Foster City, CA).

Statistical analysis

Statistical analyses were performed using GraphPad Prism 5.0 (La Jolla, CA) and SPSS v.19 (IBM Statistics). Non-parametric correlations were used, unless a linear relationship was evident.

Results

Patient characteristics

The patient characteristics are detailed in Table 1. Of the 60 patients, the majority (57%) were infected with genotype 1, were Caucasian (58%) and the average age was 52 ± 9 years. There was no gender predominance.

Temperature changes after initial PegIFN injection

After an initial PegIFN injection, oral temperature rose by 1.2 ± 0.8 °C, reaching an average peak of 37.9 °C (range 36.7–39.6 °C). In 20 patients (33%), oral temperature rose above 38.0 °C. Peak temperature was reached mostly during the evening shift, at a median of 12.5 h (range 6.4–20.4) after injection.

To compare the effect of PegIFN to the normal diurnal temperature variation, we analyzed another set of temperature measurements in 15 of the 60 patients, obtained when they were admitted to the NIH Clinical Center 6 months after stopping antiviral treatment for an additional liver biopsy. $\Delta T_{\max}$ without PegIFN was significantly lower than when the patients received PegIFN (0.4 ± 0.5 vs. 1.2 ± 0.8 °C, $p = 0.005$, paired t -test).

Association with early viral kinetics

There was a strong linear correlation between $\Delta T_{\max}$ and the 1st phase virological decline ($r = 0.59$, $p < 0.0001$, Fig. 1A) with a rise of 0.49 °C (95% CI 0.31–0.67) for each 1 log₁₀ decline in viral levels. A similar correlation was seen with the 2nd phase slope of virological decline ($r = 0.39$, $p = 0.007$, $n = 45$, Fig. 1B), but the latter association did not remain significant when adjusted for 1st phase decline ($p = 0.63$).

Use of antipyretics

Antipyretics were requested by 29 (48%) patients during the first 24-h period after PegIFN injection. Since oral administration of acetaminophen reduces temperature within 1 to 3 h of ingestion by 1 °C on average, we performed a sensitivity analysis by adding 1 °C to measurements that were performed 1–3 h after a dose of acetaminophen. The associations of the adjusted $\Delta T_{\max}$ were similar to those of the unadjusted analyses (1st phase $r = 0.59$, $p < 0.0001$; 2nd phase $r = 0.33$, $p = 0.026$, Supplementary Fig. 1). Patients who requested

antipyretics were more likely to be infected with genotypes 2/3 (45% vs. 19% of those not needing antipyretics, $p = 0.034$), were more likely to have rs12979860 CC genotype (71% vs. 36%, $p = 0.007$), and were more likely to become fast responders (62% vs. 27%, $p = 0.006$). Age, gender, BMI, race and baseline viral levels were not associated with antipyretic use.

Association with demographic factors

$\Delta T_{\max}$ did not differ between males and females (1.3 ± 0.8 °C vs. 1.2 ± 0.84 °C, $p = 0.46$) and the association of $\Delta T_{\max}$ with 1st phase decline was similar for males ($r = 0.69$, $p < 0.001$) and females ($r = 0.45$, $p = 0.013$). There was also no association between $\Delta T_{\max}$ and the presence of cirrhosis ($p = 0.61$). $\Delta T_{\max}$ differed between races ($p = 0.016$, Kruskal-Wallis test), with a statistically significant difference between Asians and Caucasians (1.8 ± 0.7 °C, vs. 0.9 ± 0.7 °C, $p = 0.009$). In African-Americans, $\Delta T_{\max}$ was not significantly different from Caucasians (1.2 °C, $p = 0.20$). The magnitude of association between $\Delta T_{\max}$ and 1st phase virological response was remarkably similar across races; every 1 $\log_{10}$ decline in viral levels was associated with a temperature increase of 0.40 °C in Caucasians, 0.41 °C in Asians, and 0.56 °C in African Americans.

Association with viral genotypes

Patients infected with genotype 2 or 3 virus had a similar rise in temperature (1.3 ± 0.9 °C) compared to genotype 1 patients (1.1 ± 0.7 °C, $p = 0.17$, Fig. 2A), despite a marked difference in 1st phase virological decline between the two groups (2.3 ± 0.8 vs. 1.2 ± 0.8 $\log_{10}$, $p < 0.0001$). The slopes of linear regression of $\Delta T_{\max}$ vs. 1st phase decline were similar for genotype 1 (slope = 0.55 [CI 0.28–0.81], $r = 0.59$, $p = 0.0002$, Fig. 2B) and for genotype 2/3 (slope = 0.75 [CI 0.33–1.16], $r = 0.68$, $p = 0.001$, Fig. 2C), suggesting that the association is independent of viral genotype. As expected, for the same $\Delta T_{\max}$, patients with genotype 2/3 infection had a greater 1st phase virological decline than that of genotype 1 patients. $\Delta T_{\max}$ was not associated with baseline HCV RNA level (Spearman's $\rho = -0.11$, $p = 0.42$).

Association with IL28B genotype

$\Delta T_{\max}$ was significantly higher for patients with the *IL28B*-related SNP rs12979860 CC genotype (1.4 ± 0.8 °C) compared to patients with CT or TT genotype (0.8 ± 0.6 °C, $p = 0.001$, Fig. 3A). Interestingly, the correlation of $\Delta T_{\max}$ with 1st phase decline was limited to patients with CC genotype (slope = 0.71 [CI 0.39–1.03], $r = 0.65$, $p < 0.0001$, Fig. 3B) whereas no association was observed in patients with CT/TT genotype (slope = 0.1 [CI -0.22 to 0.41], $r = 0.13$, $p = 0.53$, Fig. 3C). There was no association between timing of peak temperature and genotype.

Association with ISG expression

$\Delta T_{\max}$ was closely associated with serum IP10 fold-induction at 6 h ($r = 0.44$, $p = 0.005$) and at 24 h ($r = 0.47$, $p = 0.003$) after the interferon injection. As with the 1st phase decline, the association of IP10 induction with $\Delta T_{\max}$ was only seen in patients with rs12979860 CC genotype ($r = 0.6$, $p = 0.05$ for 6-h induction and $r = 0.55$, $p = 0.01$ for 24-h, Fig. 4A), while no association was seen in patients with CC/CT genotypes ($r = 0.14$, $p = 0.59$ at 6 h and $r = 0.02$, $p = 0.93$, at 24, Fig. 4B). Similarly, a positive correlation of a similar magnitude between $\Delta T_{\max}$ and the fold-induction of 4 ISGs, *CD274*, *ISG15*, *RSAD2*, and *IRF7*, in PBMCs from baseline to 6 h was seen in patients with the CC genotype ($r = 0.60$, 0.54, 0.50, and 0.50, respectively, $p < 0.05$ for all), but not in patients with the CT/TT genotype (Supplementary Fig. 2). The induction in PBMCs of *CXCL10*, the gene encoding IP10, was

not correlated with $\Delta T_{\max}$ (Supplementary Fig. 2I–J), consistent with our previous observation that serum IP10 induction reflects hepatic, and not PBMC expression [6].

The temporal pattern of serum IP10 and PBMC ISGs over the first 4 weeks of treatment was similar for all patients, but the peak of response was higher in patients who demonstrated a higher $\Delta T_{\max}$ (Supplementary Fig. 3). ISG induction in PBMCs did not differ between patients with CC or CT/TT genotype.

Independence of associations

To determine the independence of associations of baseline factors with the febrile response, we performed a fixed-effects model analysis of variance, including the variables that were associated with temperature on univariate analysis: race and rs12979860 genotype. The association of both variables with $\Delta T_{\max}$ remained significant ($p = 0.038$ for race, 0.029 for rs12979860). Since viral genotype is the strongest viral factor influencing response, we repeated the analysis with viral genotype (2/3 vs. all others) included. Race and rs12979860 retained their significant association ($p = 0.04$ and 0.027, respectively), while viral genotype was not associated with $\Delta T_{\max}$ ($p = 0.27$).

We then aimed at determining whether the association of $\Delta T_{\max}$ with 1st phase decline is independent of known predictors of virological response. To select covariates, we initially performed univariate and multivariate regressions to identify predictors of 1st phase decline other than temperature. As previously reported, we found viral genotype, host *IL28B* genotype and IP10 to predict virological response (Supplementary Table 1). We then performed a multivariate linear regression with $\Delta T_{\max}$ included, using two separate models. Model I incorporated $\Delta T_{\max}$, viral genotype and rs12989760 genotype; model II also included IP10 fold-induction at 24 h. $\Delta T_{\max}$ was a significant predictor of 1st phase virological decline in both models (Table 2), although the effect size and significance decreased when IP10 induction was added to the model, consistent with the correlation between the two and our notion that both factors reflect the same biological process of host interferon response.

Utility in predicting response to treatment

$\Delta T_{\max}$ was numerically higher in patients who achieved landmarks of virological response (Table 3) but this did not reach statistical significance. $\Delta T_{\max}$ was not a good predictor of RVR (area under the curve of ROC = 0.59, 95% CI 0.43–0.74), or SVR (0.61, 0.46–0.76). $\Delta T_{\max}$ was a weak predictor of EVR (0.68, 0.49–0.88), but did not reach statistical significance ($p = 0.084$).

Discussion

Response rates to PegIFN-based treatment of chronic hepatitis C are variable and depend on multiple parameters. Pre-treatment predictors of response include, among others, viral level, disease stage, gender, race/ethnicity, obesity [7], and, most importantly, viral genotype [8] and host *IL28B* genotype [9]. On-treatment, the major predictors of sustained response in the compliant patient are the early kinetics of virological response. In clinical practice, the response at week 12 (EVR) [10] and to a lesser degree the response at week 4 (RVR) [11] can be used to assess responsiveness and to guide treatment duration. Detailed analysis of very early kinetics demonstrated that the response pattern to a single dose of interferon is biphasic, with a rapid first phase decline and a slower second phase [5]. The response pattern to repeated dosing of pegylated interferon [12] is more complex, demonstrating a possible 3-phasic pattern with dampening of individual first phases. Although the very early

viral kinetics are predictive of ultimate response, they require very frequent sampling and are not feasible except in research setting.

Treatment with PegIFN is associated with various side-effects; some, such as fever and chills, are associated with individual injections, tend to follow a predictable temporal pattern in relation to the injection and often decrease with subsequent injections. Other side effects, like bone-marrow suppression, weight loss or depression, take longer to appear and generally, once occurred, tend to persist for the duration of treatment. The clinical features of the constitutive symptoms were suggestive of the features of the 1st phase of virological response; we therefore undertook this analysis to determine the association.

We found the temperature rise within the first 24 h after PegIFN injection to be closely correlated with the 1st phase virological response to that injection. This association was independent of virological predictors of response (viral genotype and baseline viral level) and of liver-related predictors (degree of fibrosis) but was associated with host polymorphisms for an *IL28B*-related SNP. As mathematical modeling suggests that the first phase decline is mainly affected by the effectiveness of IFN in blocking viral replication (ϵ) [5], the temperature spike after the first dose seems to reflect host responsiveness to PegIFN. The anti-viral effects of interferon are mediated through the JAK-STAT pathway and induction of interferon-stimulated genes (ISGs) [13]. The rise in temperature was correlated with the induction of ISG expression in PBMCs and of IP-10, a serum ISG, and temporally parallels the known kinetics of ISG induction, at least in patients with the favorable rs12979860 genotype.

The temperature rise was not a strong predictor of subsequent treatment response, although numerically higher values were seen in responders. This most likely reflects lack of power and the “noisy” nature of our retrospective analysis of temperature measurements. Furthermore, as antipyretics were more frequently used by patients with favorable baseline predictors of response (*IL28B* genotype and viral genotype), the diminished febrile response in these patients decreased our ability to detect an effect.

The febrile response to interferon, endogenous or exogenous [14,15], is mediated by its direct action on the hypothalamus leading to upregulation of cyclooxygenase 2 [16], and release of prostaglandin E2, a major regulator of the sickness syndrome [17]. Although the site of action of interferon for the antiviral effect, the liver, clearly differs from the hypothalamic site of the pyrogenic effect, the similarity of temporal patterns of temperature rise to known kinetics of ISG induction, and the correlation we demonstrate with ISGs, known to be associated with treatment response [18], suggests that a similar set of ISGs may be responsible for the antiviral effects and for the temperature spike.

We demonstrate a strong dependency of the association between fever and virological response on the genotype of a polymorphic locus near *IL28B*, which has been closely associated with spontaneous [19] and treatment-induced [9] recovery from chronic hepatitis C, suggesting a shared mechanism. We have recently shown that the endogenous response in the liver to HCV infection is predominantly driven by the type III IFNs (of which *IL28B*, also known as IFN- λ_3 , is a member) and that some of the ISGs are affected by type III IFNs more than by type I [20,21]. Due to restricted expression of the receptor complex, only a limited set of cell types responds to type III IFNs [22]. Neurons and astrocytes were shown to be responsive to IFN- λ [23], as are hepatocytes, and thus it is plausible that the same mechanism by which *IL28B* polymorphism modulates hepatic response to exogenous PegIFN- α , applies to the hypothalamic response as well. Whether the newly-described IFN- λ_4 [24] plays a role is unknown.

In patients with rs12989760CT/TT genotype, we were still able to detect significant virological responses and temperature increases, albeit lower in magnitude, but these were not correlated with each other. It is possible that a correlation does exist and was not significant due to a type II error; however, even if such a correlation exists, the slope of the association is definitely shallower. The rs12989760 polymorphism was shown to be associated with hepatic expression of *IL28B* and of ISGs in patients with chronic hepatitis C, with patients carrying the CT/TT genotype demonstrating higher baseline levels of ISGs [21,25]. This, in turn, could lead to a state of IFN-refractoriness which underlies the diminished virological response to treatment [26]. Our data suggest that a similar state of refractoriness may exist in the hypothalamus, although to a lesser degree, probably because the hypothalamic interferon system is not continuously stimulated like the chronically infected liver. This would explain the diminished febrile response of patients with genotypes CC/CT, as well as the decreased association with virological response. It would be interesting to study whether *IL28B* polymorphisms also affect the febrile response to acute infections, such as influenza. Interestingly, a recent genome-wide association study did not find *IL28B* genotype to be related to PegIFN-induced cytopenias, another common side-effect of treatment [27]. This is likely because the type III IFN receptor complex is not expressed on bone-marrow derived cells, and highlights the need for the presence of the receptor to modulate response to type I IFN.

The rise in temperature is unlikely to be caused directly by the virological response to treatment and the association most likely reflects two processes driven in parallel by the same factor; thus, the febrile response is a marker of the host interferon-responsiveness and not of the antiviral activity. However, the temperature increase could, at least theoretically, contribute to the immunological response against HCV following PegIFN injection, as temperature has been shown to affect activation of immune cells [28,29].

Our study is unique in that all patients received their PegIFN at exactly the same time of day, were inpatients under standard conditions and had viral kinetics measured frequently in a consistent prospective manner. However, the retrospective nature of the temperature analysis imposes inherent limitations on its interpretation. As the temperature analysis was not planned prospectively, temperatures were taken once per shift and the exact timing, as well as the use of antipyretics, was left to the nurse's discretion. As such, we are not able to calculate accurate temperature kinetics and there is a potential for bias, introduced by patients complaining of symptoms that could affect timing of temperature measurement. The use of antipyretics could decrease our ability to detect significant associations, by blunting the febrile response. Furthermore, the absence of similar temperature measurement following the subsequent PegIFN injections limits our ability to generalize our findings beyond the initial treatment dose. Despite those limitations, our study provides the largest and most accurate assessment of temperature changes post-interferon in patients with chronic hepatitis C. We found only one previous paper, in Japanese, specifically addressing characteristics of fever in chronic hepatitis C patients treated with PegIFN [30], in which similar findings regarding the pattern of fever development are described, but no observation was made regarding the association with treatment response.

In summary, we describe the features of temperature increase during the initiation of PegIFN and RBV treatment for chronic hepatitis C and demonstrate its close association with treatment response and its modulation by *IL28B* genotype. Since the spike of fever is independent of virological predictors of response, it could potentially serve in the research setting as a tool to tease out host interferon-responsiveness from viral- and liver-related factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HCV	hepatitis C virus
PegIFN	peginterferon alfa 2a
IP-10	interferon-gamma-inducible protein-10
IFN	interferon
PGE2	prostaglandin E2
ISG	interferon-stimulated gene
RVR	rapid virological response
EVR	early virological response
SVR	sustained virological response

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Fig. 1. Association between maximal rise in temperature ($\Delta T_{\max}$) and early viral kinetics
 (A) Association with 1st phase decline in HCV RNA. (B) Association with 2nd phase slope of decline.

Fig. 2. Association between $\Delta T_{\max}$ and viral genotype

(A) $\Delta T_{\max}$ in patients with HCV genotype 1 or genotypes 2/3. (B) Association of $\Delta T_{\max}$ with 1st phase decline in patients with genotype 1 or (C) genotypes 2/3.

Fig. 3. Association between $\Delta T_{\max}$ and IL28B-related rs12989760 genotype
 (A) $\Delta T_{\max}$ in patients with rs12909760CC or CT/TT genotype. (B) Association of $\Delta T_{\max}$ with 1st phase decline in patients with rs12909760CC or (C) CT/TT genotype.

Fig. 4. Association between $\Delta T_{\max}$ and serum IP-10 fold-induction 24 h after PegIFN injection (A) Patients with rs12909760CC genotype. (B) Patients with rs12909760CC/CT genotype.

Table 1

Patient characteristics.

Sex (male/female)	30/30 (50%/50%)
Age (mean $\pm$ S.D.)	52 $\pm$ 9
Race	
Caucasian	58%
African American	22%
Asian	18%
Mixed	2%
rs12989760 genotype (n = 56)	
CC	54%
CT	29%
TT	18%
Liver fibrosis (n = 51)	
Mild	63%
Bridging	18%
Cirrhosis	20%
HCV genotypes	
1	57%
4, 5, 6	10%
2, 3	33%
Treatment response	
Fast	42%
RVR	28%
EVR	83%
SVR	38%

Table 2

Multivariate linear regression for 1st phase decline.

Predictor	Regression Coefficient	95% CI	<i>p</i> value
Model I			
$\Delta T_{\max}$ (°C)	0.46	0.17–0.59	0.003
HCV genotype 2/3 vs. all others	0.89	0.48–1.29	<0.001
rs12989760 CC vs. CT/TT	0.45	0.01–0.89	0.046
Model II			
$\Delta T_{\max}$ (°C)	0.30	0.014–0.59	0.041
HCV genotype 2/3 vs. all others	0.69	0.30–1.08	0.001
rs12989760 CC vs. CT/TT	0.46	0.07–0.86	0.024
IP10 fold-induction 0 to 24 hr (log-transformed)	0.11	0.03–0.19	0.007

Table 3 $\Delta T_{\max}$ and treatment response.

	Yes	No	<i>p</i> value
Fast response	1.3 ± 0.8 (n = 26)	1.0 ± 0.7 (n = 33)	0.14
RVR	1.3 ± 0.8 (n = 17)	1.1 ± 0.8 (n = 42)	0.29
EVR	1.2 ± 0.8 (n = 50)	0.8 ± 0.7 (n = 9)	0.11
SVR	1.4 ± 0.9 (n = 30)	1 ± 0.6 (n = 23)	0.15