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ORIGINAL RESEARCH ARTICLE

Differential Antiviral Effects of Pegylated Interferon-α_{2a} and Pegylated Interferon-α_{2b} in Chronic Hepatitis C

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Abstract

Background and Objectives Pegylated interferon (peg-IFN)-α_{2a} and -α_{2b} show different pharmacokinetic properties but are used interchangeably for hepatitis C treatment in traditional dual combinations and with newer agents. We assessed whether peg-IFN antiviral effects vary with peg-IFN subtype, affecting viral response in a differential manner.

Methods Chronic hepatitis C patients treated with ribavirin combined with peg-IFN-α_{2a} ($N = 109$) or -α_{2b} ($N = 114$) were studied. Hepatitis C virus RNA quantitation was performed by Cobas TaqMan 5 min before treatment start and subsequently after 48/72 h and 7, 14, 28 and 90 days. Antiviral effect was assessed in terms of viraemia changes over treatment. Histology grading and staging, interleukin-28B (*IL28B*) status and baseline viral genotype, alanine aminotransferase, gamma glutamyltransferase and glucose were analysed.

Results Viraemia decline after 48/72 h and 7 days was significantly greater with peg-IFN-α_{2b} (1.96 and 2.12 vs 1.49 and 1.20 $\log_{10}$ IU/mL with peg-IFN-α_{2a}; $p < 0.001$). Differences were of larger extent in patients with advanced fibrosis ($p = 0.002$), genotype 1 infection ($p = 0.002$) and CT/TT genotypes of *IL28B* ($p = 0.001$). A rebound in viral load was observed significantly more often after the first dose in patients treated with peg-IFN-α_{2b} (78 vs 28 % in those with peg-IFN-α_{2a}; $p = 0.0001$). Differences between peg-IFNs disappeared by day 28 of treatment.

Conclusion There are significant pharmacodynamic differences between peg-IFN-α_{2a} and -α_{2b} in the early phase of chronic hepatitis C treatment. The greater early viral decline observed with peg-IFN-α_{2b} was essentially confined to 'difficult to treat' patients. Whether this could affect response-guided treatment decision making, as well as triple drug regimens, needs to be assessed.

Key Points

The very early initial decline of hepatitis C virus RNA is significantly greater with pegylated interferon (peg-IFN)-α_{2b} compared with peg-IFN-α_{2a}.

A rebound in viral load at the end of the first dosing interval occurs significantly less often with peg-IFN-α_{2a}.

After the first 2–4 weeks of therapy, no differences between peg-IFN subtypes are evident.

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1 Introduction

The current treatment for chronic hepatitis C (CHC) essentially still hinges on the combination of pegylated

interferon (peg-IFN)-α and ribavirin [1]. This association allows achievement of a sustained viral response (SVR), defined as undetectable hepatitis C virus (HCV) RNA in blood 24 weeks after completion of therapy, in about 55 % of patients [2–4].

Two options are currently available for CHC treatment, namely peg-IFN-α_{2a} and peg-IFN-α_{2b}, showing a molecular weight of 40 and 12 kDa, respectively. Peg-IFNs show different pharmacokinetic properties, which affect absorption, serum half-life and excretion. Data from comparative and noncomparative studies suggest that peg-IFN-α_{2b} has a shorter serum half-life, whilst peg-IFN-α_{2a} is absorbed more slowly and has a smaller volume of distribution, being confined largely to blood and liver compartments [5, 6]. Also, peg-IFN-α_{2b} appears to reach subtherapeutic levels at the end of the dosing interval [5]. Based on these differences, several studies have tried to assess whether pharmacodynamic differences or clinical superiority of one peg-IFN over the other exist.

In the largest comparative trial (IDEAL), rapid viral response (RVR) rates, defined as undetectable HCV RNA at week 4 of treatment, did not differ between peg-IFN arms (12.2 vs 12.1 %). In contrast, early viral response (EVR) rates were significantly higher with peg-IFN-α_{2a} [7]. In the observational PRACTICE study, no differences in SVR rates were noted in the intent-to-treat cohort (52.9 vs 50.5 %), although genotype 1-infected patients had a higher SVR with peg-IFN-α_{2a} (49.6 vs 43.7 % with peg-IFN-α_{2b}) [8]. Peg-IFN-α_{2a} was associated with improved EVR and SVR compared with peg-IFN-α_{2b}, without differences in RVR rates, in a randomized study [9]. These results were mirrored by those of another independent study [10].

Viral decline as measured in serial serum samples is the most accurate measure of peg-IFN pharmacodynamics [11].

Both types of peg-IFN, when associated with ribavirin, induce a biphasic viral decline, where the first phase (24–72 h) is rapid and dose dependent, and the second phase (from day 3) is highly variable and shows a much slower decline [12]. The rate of serum HCV RNA decline on therapy is also a strong predictor of SVR. Patients who achieve RVR consistently show a higher probability of SVR [13]. The first phase of HCV RNA decline is already strongly predictive of the final outcome of therapy [14, 15]. However, few data are available regarding the first phase of viral decline, as a pharmacodynamic parameter, according to the actual peg-IFN subtype employed.

Thus, in this study, we assessed whether peg-IFN antiviral effect varies, affecting viral response in a differential manner. The main study objective was to analyse the impact of the peg-IFN subtype on the early serum HCV RNA kinetics. Secondary end points were the percentages of SVR, nonresponse (NR) and relapse 24 weeks after treatment end.

2 Patients and Methods

2.1 Study Sample

Included in this retrospective, observational study were 223 CHC patients, treated in our unit between 2007 and 2013 with peg-IFN and ribavirin according to a standardized clinical protocol. The study cohort included men and women who had (1) alanine aminotransferase (ALT) levels above the upper limit of normal on at least one occasion during the preceding 2 years; and (2) detectable serum HCV RNA. A diagnostic liver biopsy was performed within 3 years of treatment start to assess necro-inflammatory grade, fibrosis stage and presence and extent of steatosis in 185 patients (83 %). Excluded were patients with persistently normal ALT; other causes of liver disease; hepatitis B and human immunodeficiency virus co-infection; clinically overt autoimmune diseases; and suboptimal adherence to treatment. Adherence to treatment was assessed by regular checks of drug prescription and pharmacy dispensation logs and personal injection of the first five doses of peg-IFN to each patient. Informed consent for data collection and additional blood sampling for viraemia determination was obtained from all patients before starting treatment. All procedures were in accordance with the Declaration of Helsinki and the study protocol was approved by our institutional review board.

2.2 Analytical Procedures

Among the laboratory parameters measured at baseline, serum levels of glucose, ALT and gamma glutamyltransferase (gamma GT) were recorded and included in the analysis. 'Hyperglycaemia' was defined as a pretreatment serum level of glucose ≥6 mmol/L after overnight fasting or a prior diagnosis of diabetes mellitus. Serum HCV RNA concentrations were measured by Cobas TaqMan (Roche Diagnostics, Milan, Italy), with a detection limit of 10 IU/mL. Interleukin-28B (*IL28B*) rs12979860 polymorphism was analysed by real-time polymerase chain reaction (PCR) (LightMix®, Roche Diagnostics, Milan, Italy) in 141 of 223 patients (63.2 %).

2.3 Antiviral Treatment Protocol and Definition of Response

The treatment regimen consisted of either peg-IFN-α_{2a} (Pegasys, Roche, 180 mcg subcutaneously once a week) or peg-IFN-α_{2b} (Peg-Intron, Merck, 1.5 mcg per kilogram of

body weight subcutaneously once a week), as chosen by the physician in charge. As the flu-like syndrome after the first dose is more intense with peg-IFN-α_{2b}, this was avoided in less motivated patients. Moreover, flat-dose peg-IFN-α_{2a} was prescribed only to patients with 'average' body weight, whereas outliers (either <60 or >90 kg) were mostly given weight-based peg-IFN-α_{2b}. All subjects received combination treatment with ribavirin, at the dose of 800 mg/day (400 mg twice a day) for those infected with HCV genotype 2 or 3 and 1,000 or 1,200 mg/day for subjects infected with genotype 1 weighting <75 or ≥75 kg, respectively. The predetermined length of treatment was 48 weeks for genotype 1 and 24 weeks for genotype 2 and 3 patients.

SVR was defined as undetectable (<10 IU/mL) HCV RNA on real-time PCR 24 weeks after the end of treatment. Viral relapse was defined as reversion to HCV RNA-positive status in a patient who had an undetectable HCV RNA level (<10 IU/mL) at the end of treatment. NR was defined as an HCV RNA decrease lower than 2 $\log_{10}$ IU/mL from baseline by week 12 of therapy.

2.4 HCV RNA Kinetics Analysis

HCV RNA decline was assessed in all patients at either 48 or 72 h, and subsequently at 7, 14, 28 and 90 days after treatment start. Viraemia levels were compared with the baseline value, obtained on a blood sample taken 5 min before the first peg-IFN dose. As a measure of the early HCV RNA kinetics, the $\log_{10}$ HCV RNA decline was calculated, i.e. the difference between baseline and day 2 or 3 $\log_{10}$ HCV RNA levels. The same determinations were done for day 7, 14 and 28 after treatment start.

2.5 Statistical Analysis

Data are presented as median and range or number and percentage. Differences between groups treated with different peg-IFNs were analysed by Fisher's exact test or Chi-square test for categorical variables. Mann–Whitney *U* test was used to compare numerical variables. *P* values <0.05 were considered statistically significant. Analyses were done using SPSS software, version 16.

3 Results

3.1 Baseline Patient Features

A total of 223 patients were studied, of whom 56 % were males, and with a median age of 56 years. In one fourth of patients, liver biopsy showed a cirrhotic liver. Patients were divided into two groups: 109 patients (48.9 %) who received peg-IFN-α_{2a} and 114 patients (51.1 %) who were given peg-IFN-α_{2b}. As shown in Table 1, the two groups were homogeneous for prevalence of cirrhosis, pretreatment serum HCV RNA and viral genotype distribution. The proportion of *IL28B* CC genotype was also very similar, although this genetic parameter was not available in all cases (Table 1).

3.2 Outcomes of Treatment

Table 2 shows the details of treatment response in patients grouped according to the peg-IFN subtype received. SVR was achieved by 56 and 57 % of patients in the peg-IFN-α_{2a} and -α_{2b} subgroups, respectively. There were no significant differences between groups in terms of relapse rates or treatment NR. In addition, RVR and complete early viral response (cEVR) were essentially the same (Table 2).

Table 1 Baseline clinical and virological data in the two patient subgroups studied

Characteristic	Peg-IFN-α_{2a}	Peg-IFN-α_{2b}	*p* value
N	109	114	–
Age, years	56 [20–72]	53 [19–69]	0.465
Males	65 (59 %)	63 (55 %)	0.617
HCV RNA, $\log_{10}$ IU/mL	5.981 logs	6.076 logs	0.257
HCV genotype			0.640
1	57 (52.3 %)	62 (54.4 %)	
2	39 (35.8 %)	43 (37.7 %)	
3	13 (11.9 %)	9 (7.9 %)	
IL28B[a]			0.985
CC	19 (34.5 %)	28 (32.6 %)	
CT	28 (51 %)	45 (52.3 %)	
TT	8 (14.5 %)	13 (15.1 %)	
Liver cirrhosis[b]	25 (22.9 %)	31 (27.1 %)	0.462
Liver steatosis, % of hepatocytes[b]			0.256
S1	10 [5–30]	15 [5–30]	
S2	50 [40–60]	50 [35–60]	
S3	90 [70–90]	70 [70–90]	
Alanine aminotransferase, × ULN	3.0 [0.4–12]	2.0 [0.3–9]	0.123
Gamma glutamyltransferase, IU/mL	42 [5–227]	32 [3–210]	0.027
Fasting plasma glucose, mmol/L	5.3 [3.7–12.6]	5.4 [3.9–12.1]	0.402

Data are median [range] or number (percentage)

HCV hepatitis C virus, *IL28B* interleukin-28B, *peg-IFN* pegylated interferon, *ULN* upper limit of normal

[a] *IL28B* genotyping was available in 55 and 86 patients in the peg-IFN-α_{2a} and -α_{2b} groups, respectively

[b] Liver histology was available in 88 and 97 patients in the peg-IFN-α_{2a} and -α_{2b} groups, respectively

Table 2 Treatment response according to pegylated interferon (peg-IFN) subtype administered

Parameter	Peg-IFN-α_{2a}	Peg-IFN-α_{2b}	*p* value
N	109	114	–
RVR	58 (53.2 %)	59 (51.7 %)	0.893
cEVR	68 (62.3 %)	65 (57.1 %)	0.494
SVR	62 (56.8 %)	66 (57.8 %)	0.900
NR	26 (23.8 %)	28 (24.5 %)	0.900
Relapse	15 (13.7 %)	19 (16.6 %)	0.900

Data are number (percentage)

cEVR complete early viral response, *NR* nonresponse, *RVR* rapid viral response, *SVR* sustained viral response

3.3 Early Antiviral Effects and Peg-IFN Subtype

When we moved on to analyse the very early treatment effect, i.e. the initial viral kinetics, according to the peg-IFN subtype received, differences were observed. As the number of patients with viraemia determination at 48 and 72 h was significantly different between peg-IFN subtypes (peg-IFN-α_{2a} 53 and 56 patients; peg-IFN-α_{2b} 79 and 35 patients; $p = 0.003$), we assessed the results at these two different time points separately.

Changes in HCV RNA kinetics over the first 4 weeks of therapy are graphically shown in Fig. 1. In both groups, a drop of viraemia was observed, but this was significantly greater at both 48 and 72 h (first-phase kinetics) and at 7 days of treatment with peg-IFN-α_{2b} (Fig. 1). In fact, the median decline of viraemia was 1.96, 2.01 and 2.12 $\log_{10}$ IU/mL after 48 h, 72 h and 7 days, respectively, in patients treated with peg-IFN-α_{2b}, a reduction that was significantly higher ($p < 0.001$) compared with that observed in patients treated with peg-IFN-α_{2a} (1.49, 0.99 and 1.20 $\log_{10}$ IU/mL). Viraemia suppression remained significantly greater with peg-IFN-α_{2b} up to day 7. However, differences between peg-IFN subgroups started to lessen at day 14 after treatment start and completely disappeared by day 28 of treatment, suggesting the subsequent pharmacodynamic effects were similar in the two groups (Fig. 1). In order to obtain a further measure of the antiviral effects of peg-IFNs, we measured the slopes depicting the median HCV RNA drop from baseline to either 48 or 72 h in the two subgroups. Peg-IFN-α_{2b} slope was significantly steeper than that of peg-IFN-α_{2a} (data not shown).

3.4 Modifiers of the Antiviral Effect According To Peg-IFN Subtype

The differences between the two peg-IFNs were further assessed in relation to viral genotype, *IL28B* polymorphism, liver fibrosis and steatosis, serum ALT and gamma GT levels, as well as glucose metabolism. As shown in Fig. 2, a significant difference in the extent of HCV RNA decline over the first 48/72 h of therapy was evident mostly for genotype 1, much less so for genotypes 2 and 3. Moreover, a statistically significant difference was observed between peg-IFN subgroups in terms of early effects in *IL28B* CT/TT patients, whilst only a trend for a greater effect of peg-IFN-α_{2b} was evident in CC patients (Fig. 2).

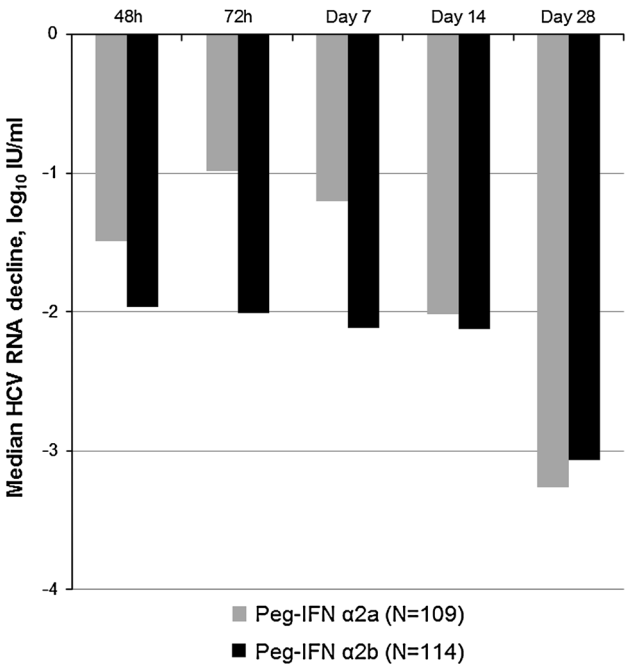

Fig. 1 Extent of the hepatitis C virus (HCV) RNA drop at the different time points after treatment start in the two pegylated interferon (peg-IFN) subgroups

We also looked at the influence of the other major host factors affecting viral response according to the peg-IFN subtype used. As shown in Fig. 3a, the greater early effect of peg-IFN-α_{2b} emerged only for patients with advanced fibrosis ($p = 0.002$). After excluding genotype 3 patients, steatosis was confirmed to be associated with a smaller early decline of viraemia (Fig. 3b). Peg-IFN-α_{2b} had a greater early effect than peg-IFN-α_{2a} irrespective of the extent of steatosis. Serum gamma GT levels were also confirmed to be indirectly related to the extent of the early HCV RNA decay (Fig. 3c). A trend for a greater effect of peg-IFN-α_{2b} was observed in patients with the highest quartiles of gamma GT levels. Similar results emerged for serum ALT levels, with a larger HCV RNA drop in patients with lower pretreatment ALT values, but irrespective of the peg-IFN subtype employed (Fig. 3d).

We finally analysed the effect of glucose metabolic status on peg-IFNs antiviral action. As depicted in

Fig. 4, normoglycaemic subjects experienced better responses compared with patients with hyperglycaemia. Interestingly, however, the reduced early efficacy of treatment in hyperglycaemic individuals was evident only with peg-IFN-α_{2a}, but could not be detected with peg-IFN-α_{2b}.

3.5 Viral Rebound

When we compared day 7 viraemia with that measured at either 48 or 72 h in individual subjects, a rebound in viral load was observed significantly more often in patients treated with peg-IFN-α_{2b} (78 vs 28 % in those with peg-IFN-α_{2a}; $p = 0.0001$), suggesting a failure of peg-IFN-α_{2b} to maintain its antiviral activity at the end of the first dosing interval. When these patterns were evaluated in the whole study sample according to the viral genotype and the *IL28B* polymorphism, we observed that the extent of day 7 HCV RNA rebound was 63 and 37 % in G1 vs G2/3 patients and 68 and 32 % in CT/TT and CC carriers.

4 Discussion

The results of this retrospective study indicate that the antiviral effect of the two available peg-IFN subtypes is substantially different during the initial phases of antiviral treatment. In particular, peg-IFN-α_{2b} is faster in abating viraemia, at least over the first 7 days of therapy. However, its use is associated with a high rate of viral rebound before the second dose is given. Besides of these differences, the subsequent antiviral effectiveness of the two different peg-IFN subtypes is overall the same and in our experience equal cure rates are achieved in combination with ribavirin.

The extent of HCV RNA decay during the first weeks of treatment depends on a number of viral and host factors, including HCV genotype, initial viral load, stage of liver fibrosis, extent of liver necro-inflammation and steatosis, and insulin resistance [16, 17]. Several studies have analysed the predictive value of the HCV RNA decline in terms of treatment outcome [18, 19]. Fewer studies have assessed the differential effect of peg-IFN-α_{2a} and -α_{2b} on this decline, a parameter that is revealing in terms of peg-

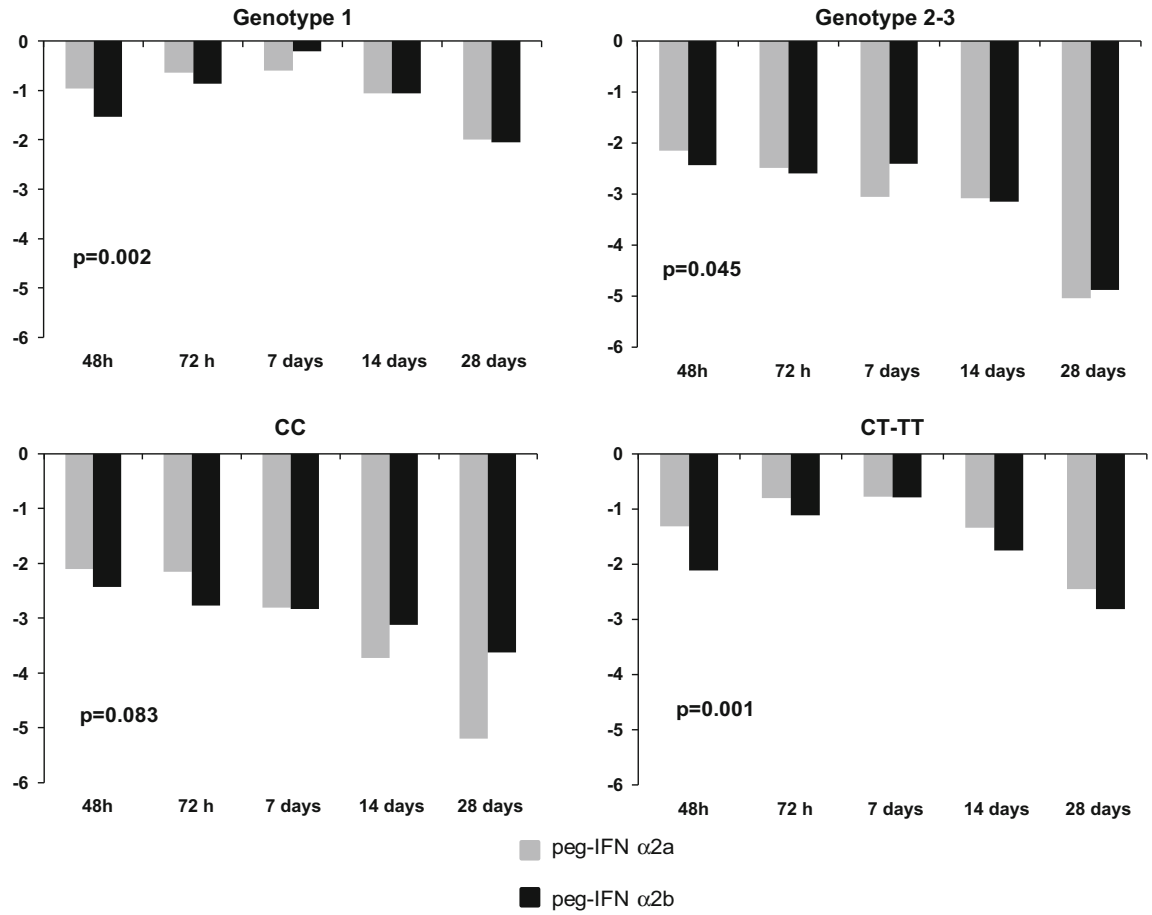

Fig. 2 Comparison of the median slopes of hepatitis C virus RNA decrease from baseline up to day 28 of therapy with pegylated interferon (peg-IFN)-α_{2a} and -α_{2b}. Comparisons are shown for patients grouped according to genotype (*top*) and interleukin-28B polymorphism (*bottom*) (CC homozygotes and CT heterozygotes plus TT homozygotes)

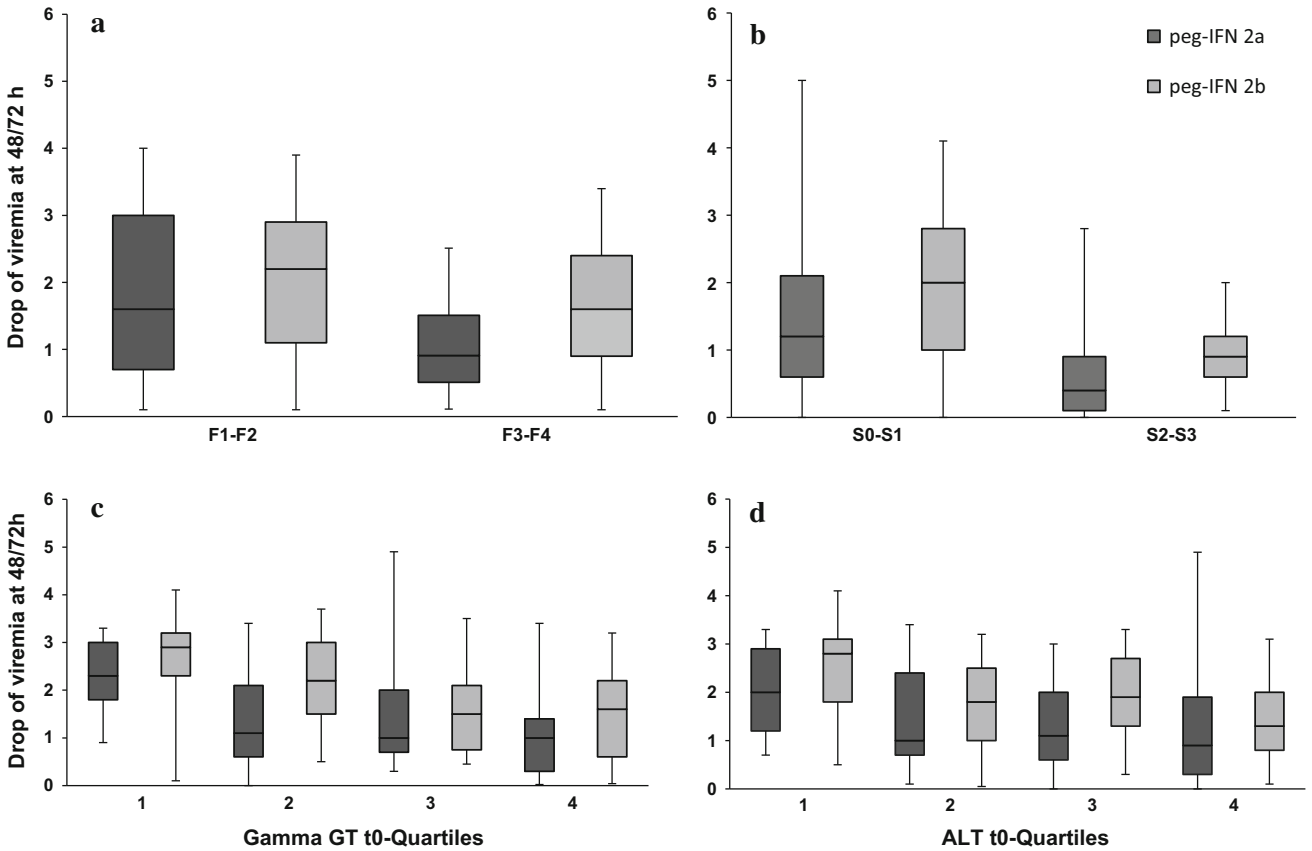

Fig. 3 Early kinetics of hepatitis C virus RNA with the two different pegylated interferon (peg-IFN) subtypes used according to the major host factors affecting viral response: **a** liver fibrosis, categorized as mild/moderate (F1–F2) and advanced (F3–F4); **b** liver steatosis, classified as absent/mild (S0–S1) and moderate/severe (S2–S3); **c** gamma glutamyltransferase (gamma GT) levels, divided in quartiles; **d** alanine aminotransferase (ALT) levels, divided in quartiles. *Boxes* represent the interquartile 25th–75th range, the *central line* the median, the *whiskers* the minimum and maximum values of the data distribution

IFN pharmacodynamics. We here show that the peg-IFN subtype matters during the early phases of therapy and that this needs to be taken into account.

Indeed, a potential implication of HCV RNA kinetic evaluation includes the possibility of individualizing therapy by adding another drug to the traditional regimen. This is currently being pursued with the protease inhibitors telaprevir and boceprevir, and more recently sofosbuvir in genotype 1 patients. These potent direct acting antivirals may induce resistance, so their use must be 'protected' by a peg-IFN and ribavirin backbone. Our data indicate that in these settings, it is of utmost importance to define which peg-IFN subtype is used. Indeed, as peg-IFN-α_{2b} purports to have a deeper early suppression of viraemia, it could appear as a better option to 'protect' protease inhibitors. However, the common rebound in viraemia that is observed with this molecule at day 7 strongly suggests that its antiviral effect vanishes at the end of the first dosing interval, possibly exposing the added drug to the risks of a 'functional' monotherapy.

The retrospective nature of this analysis and the absence of a randomized design are limitations of our study, although the two groups were very well matched for baseline parameters. In contrast, together with the considerable number of subjects assessed, the homogeneity of our cohort and procedures applied represents a strength of our work. Another study is available in the literature [20] that has analysed the early HCV RNA kinetics according to the peg-IFN subtype. In this Japanese investigation, a faster HCV RNA decline was observed in the group treated with peg-IFN-α_{2a}, at variance with our data. However, our observations are in line with all prior pharmacokinetic data, showing the 12 kDa peg-IFN-α_{2b} is absorbed more quickly, is cleaved to its pharmacologically active form faster and is excreted sooner, reaching subtherapeutic plasma levels at the end of the dosing interval [5, 21]. Also, our data are consistent with the results of the COMPARE study, where a significantly greater mean $\log_{10}$ HCV RNA decrease from baseline was observed in patients treated with peg-IFN-α_{2b} compared with peg-IFN-α_{2a} at weeks 4 and 8 [22].

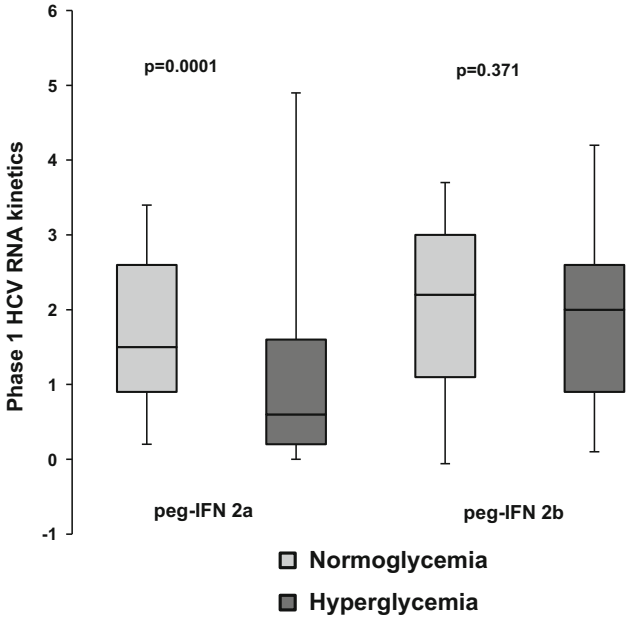

Fig. 4 Early kinetics of hepatitis C (HCV) RNA with the two different pegylated interferon (peg-IFN) subtypes used according to the actual fasting plasma glucose value (normoglycaemia <6 mmol/L; hyperglycaemia ≥6 mmol/L or known diabetes on hypoglycaemic treatment) upon antiviral treatment start. *Boxes* represent the interquartile 25th–75th range, the *central line* the median, the *whiskers* the minimum and maximum values of the data distribution

5 Conclusion

The early pharmacodynamic effect of peg-IFN is different according to the subtype used. Viraemia decreases earlier with peg-IFN-α_{2b}, although a rebound after the first dose is less often observed with peg-IFN-α_{2a}. Whether this could affect response-guided treatment decision making, as well as triple drug regimens, needs to be further assessed, as peg-IFN use will likely still be required because of specific patient conditions or the need to reduce costs [23].

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