



Neutralizing antibodies to interferon alpha and circulating Interferon in chronic hepatitis C patients non-responding to pegylated interferon plus ribavirin re-treated by Peg-Interferon alpha-2a and ribavirin (ANRS HC16 GAMMATRI substudy*)

Philippe Halfon, Sophie Pérusat, Marc Bourlière, Jean-Pierre Bronowicki, Pascale Trimoulet, Yves Behnamou, Vincent Leroy, Patrick Marcellin, Juliette Foucher, Guillaume Pénaranda, et al.

► **To cite this version:**

Philippe Halfon, Sophie Pérusat, Marc Bourlière, Jean-Pierre Bronowicki, Pascale Trimoulet, et al.. Neutralizing antibodies to interferon alpha and circulating Interferon in chronic hepatitis C patients non-responding to pegylated interferon plus ribavirin re-treated by Peg-Interferon alpha-2a and ribavirin (ANRS HC16 GAMMATRI substudy*). Journal of Medical Virology, 2010, 82 (12), pp.2027. 10.1002/jmv.21909 . hal-00589434

HAL Id: hal-00589434

<https://hal.science/hal-00589434>

Submitted on 29 Apr 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Neutralizing antibodies to interferon alpha and circulating Interferon in chronic hepatitis C patients non-responding to pegylated interferon plus ribavirin re-treated by Peg-Interferon alpha-2a and ribavirin (ANRS HC16 GAMMATRI substudy*)

Journal:	<i>Journal of Medical Virology</i>
Manuscript ID:	JMV-09-1707.R2
Wiley - Manuscript type:	Research Article
Date Submitted by the Author:	04-Jun-2010
Complete List of Authors:	Halfon, Philippe Pérusat, Sophie Bourlière, Marc Bronowicki, Jean-Pierre Trimoulet, Pascale; CHU de Bordeaux, Virologie; Université Victor Ségalen, Virologie EA2968 Behnamou, Yves Leroy, Vincent Marcellin, Patrick; hôpital beaujon, hepatology Foucher, Juliette; CHU de Bordeaux, Virologie Pénaranda, Guillaume; Laboratoire Alphabio Chene, Geneviève Couzigou, Patrice; CHU de Bordeaux, Virologie
Keywords:	second line treatment, neutralizing antibody, hepatitic C, non-responders



Neutralizing antibodies to interferon alpha and circulating interferon in patients with chronic hepatitis C non-responding to pegylated interferon plus ribavirin re-treated by pegylated interferon alpha-2a and ribavirin (ANRS HC16 GAMMATRI substudy*)

Authors: Philippe Halfon (1), Sophie Pérusat (2), Marc Bourlière (3), Jean-Pierre Bronowicki (4), Pascale Trimoulet (5), Yves Benhamou (6), Vincent Leroy (7), Patrick Marcellin (8), Juliette Foucher (5), Guillaume Penaranda (1), Geneviève Chêne (2, 5), Patrice Couzigou (5) and the ANRS HC16 GAMMATRI study group

- 1 Alpha Bio, Marseille, Hospital Ambroise Paré, France;
- 2 INSERM, U897, Bordeaux, France;
- 3 St Joseph Hospital, Marseille, France;
- 4 Brabois Hospital, Nancy, France;
- 5 Centre Hospitalier Universitaire (CHU) Bordeaux, France;
- 6 Pitié-Salpêtrière Hospital, Paris, France;
- 7 Albert Michallon Hospital, Grenoble, France;
- 8 Beaujon Hospital, Clichy, France;

Running Head: Gammatri study

Correspondence to:

Pr Philippe Halfon, MD PhD
Laboratoire Alphabio, 23 rue Friedland, Hôpital Ambroise Paré, F-13006 Marseille, France
Tel: (+33) 4 91 25 41 00 Fax: (+33)4 91 79 20 44; Mail: philippe.halfon@alphabio.fr

List of Abbreviations:

PEG: pegylated; IFN: interferon; RIBA, ribavirin; NR: non-responders to a second line treatment.

Abstract

A lack of antiviral response in patients with chronic hepatitis C treated with pegylated (PEG)-interferon (IFN) α -2a + ribavirin (RIBA) may be explained by neutralizing antibodies to IFN α -2a. The aim of the study was to assess neutralizing antibodies to IFN α -2a and IFN levels in non-responder patients who were re-treated by PEG IFN α -2a and RIBA for 12 weeks.

Non-responders to a first-line treatment of PEG IFN α -2a + RIBA were included for treatment with PEG IFN α -2a (180 μ g/week) + RIBA (1000 mg/d if <75 kg, 1200 mg otherwise) for 48 weeks. HCV RNA was measured at week 12. IFN levels and neutralizing antibodies to IFN α -2a were measured retrospectively on stored sera at baseline and weeks 4 and 12, using a quantitative sandwich ELISA for neutralizing antibodies to IFN α -2a.

Twenty-three patients were non-responders and 19 patients were responders at week 12 of the initial phase of the second-line treatment. Non-responders and responders did not differ statistically: baseline age (median age 47 vs. 50 years), HCV RNA (median 6.8 vs. 6.4 log₁₀ copies/ml), gender (70% vs. 73% males), genotype (genotype 1: 91% vs. 80%). The median IFN α -2a levels (pg/ml) at weeks 0, 4, and 12 (interquartile range) did not differ between the 19 responders to initial phase of second line treatment and the 23 non-responders :< 3.3 (<3.3- 371.4), 1457.3 (106.8- 3284.8), and 1652 (90.8- 5000); 84.5 (3.3- 277.4), 1407.4 (120.2- 2443.4), and 1620.1 (120.2- 2287.1) respectively.

Among non-selected consecutive non-responder patients, re-treatment with PEG IFN α -2a + RIBA is associated with virological response regardless of the presence of antibody-mediated resistance to conventional IFN treatment.

Key words: Second line treatment; Neutralizing antibody; Hepatitis C virus; Non-responders

INTRODUCTION

Chronic hepatitis C is a major cause of liver disease, with worldwide prevalence estimated at 3% [WHO., 2000]. Only a minority of those infected spontaneously clear HCV. Of patients who become chronic carriers, 70–80% may progress to cirrhosis and hepatocellular carcinoma [Hoofnagle, 2002; Micallef et al., 2006; Thomas and Seeff, 2005].

Response to interferon (IFN) α -2a and ribavirin (RIBA) combination therapy for the treatment of chronic hepatitis C viral (HCV) infection varies largely among patients. Indeed, with a combination of pegylated (PEG) IFN α -2a or α -2b plus RIBA for 24 or 48 weeks depending on genotype, currently the standard of care for patients with chronic hepatitis C, up to 50-60% of patients are non-responders or experience relapse after treatment ends [Seeff, 2002]. Many hypotheses have been proposed to explain the absence of response to IFN. Recent data suggest that host genetics may be useful for predicting drug response, and they also support the notion that IL28B could play a role in the treatment of HCV and in other diseases treated with IFN [Ge et al., 2009; McCarthy et al.; Rauch et al., 2010; Suppiah et al., 2009; Thomas et al., 2009].

A possible explanation for the lack of response is the development of neutralizing antibody to interferon, as shown in case series [van der Eijk et al., 2006]. There have not been reports so far on large unselected series of re-treated patients to study formally the association between neutralizing antibody and the response to treatment.

In the setting of a clinical trial, relationships were assessed between either IFN (endogenous or not) or neutralizing antibody to IFN α -2a levels and virological response to a second-line treatment with PEG IFN α -2a + RIBA.

PATIENTS AND METHODS

Patients: In a phase II, multicentric, non-comparative trial (ANRS HC16 GAMMATRI), patients received PEG IFN α -2a (180 μ g/week) in combination with RIBA (1000 mg/d if <75 kg, 1200 mg otherwise) for 48 weeks. IFN gamma-1b was added to this combination if patients did not experience a virological response at the 12-week visit, defined as a decrease in HCV RNA greater than 2 log₁₀ copies/ml relative to the

baseline. The current study included serum samples during the first 12 weeks when patients received PEG IFN α -2a and RIBA exclusively.

Adult patients (18-70 years) were eligible if they had chronic hepatitis C, were non-responders to a previous treatment with PEG IFN and RIBA (at least 12 weeks without treatment change and stopped at least 3 months before enrolment), had a Metavir histological score \geq F2, and signed a written informed consent. The protocol was approved by the ethics committee of Haut Lévêque hospital (Pessac, France), and was conducted in compliance with the Declaration of Helsinki.

For this study, the definition of treatment response was a decrease in HCV RNA greater than 2 log₁₀ copies/ml at week 12 relative to baseline values. Another criterion of treatment response was undetectable HCV RNA at week 12 or 28.

Measurements: HCV RNA was measured at week 12 using TaqMan PCR (Roche Diagnostics) (lower limit of detection 15 UI/ml) in a central laboratory to assess early response. IFN levels and neutralizing antibody to IFN α -2a were retrospectively measured on stored sera at baseline and weeks 4 and 12. Measurements were performed by technicians who were blinded to the individual response to treatment. Neutralizing antibodies to IFN α -2a were determined using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) for antibodies directed to IFN α -2a (Bender Med- Systems Diagnostic) with a limit of detection at 1.38 ng/ml. IFN α -2a levels were measured using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) for IFN α -2a (Bender Med- Systems Diagnostic) with a limit of detection at 3.3 pg/ml. For the computation of statistical parameters, undetectable values were assigned a value of zero.

Statistical analysis: Fisher's exact or Chi-square tests were used to compare proportions. The non-parametric Wilcoxon test was used to compare medians. All calculations were assessed using SAS V9.1.3 software (SAS Institute Inc. Cary, NC)

RESULTS

Twenty-three patients were non-responders and 20 patients were responders at week 12 to the initial phase of second-line treatment. Levels of IFN α -2a and neutralizing

antibody to IFN α -2a could be measured in all the patients, except for one responder who had no stored serum available and was excluded from the analysis. Non-responders and responders to the initial phase of the second-line treatment did not differ statistically: baseline age (median age 47 vs. 50 years), HCV RNA (median 6.8 vs. 6.4 log₁₀ copies/ml), gender (70% vs. 73% males), genotype (genotype 1: 91% vs. 80%). The median IFN α -2a levels (pg/ml) at weeks 0, 4, and 12 (interquartile range) did not differ between the 19 responders to initial phase of second line treatment and the 23 non-responders :< 3.3 (<3.3-371.4), 1457.3 (106.8-3284.8), and 1652 (90.8-5000); 84.5 (3.3-277.4), 1407.4 (120.2-2443.4), and 1620.1 (120.2-2287.1) respectively. Levels reached at weeks 4 and 12 were in the therapeutic range and indicated exposure to exogenous IFN. Neutralizing antibody levels were detectable among 3/19 responders (16%) vs. 5/23 non-responders (22%) (p=0.70) at week 0, among 6/19 responders (32%) vs. 6/23 non-responders (26%) (p=1.0) at week 4, and among 7/19 responders (37%) vs. 6/23 non-responders (26%) at week 12 (p=0.73) (**Table 1**). Of note in one responder, neutralizing antibody to IFN α -2a was present at week 0 and week 4 but not at week 12.

Among 5 of the 6 non-responders with neutralizing antibody to IFN α -2a, neutralizing antibody levels were detectable from week 0 to week 12, and for one of the non-responders they were detectable at week 4 and week 12. All responders and non-responders who had neutralizing antibody to IFN α -2a had undetectable endogenous IFN at week 0. There was no association between the presence of neutralizing antibody to IFN α -2a and endogenous IFN; only one patient who had endogenous IFN at baseline had neutralizing antibody to IFN α -2a. In addition, there was no significant association between the presence of endogenous IFN α -2a at baseline without any exogenous IFN α -2a and response to treatment (p=0.057).

At week 28, nine patients had undetectable HCV RNA: three of the patients had neutralizing antibody to IFN- α at week 12 and one had neutralizing antibody to IFN α -2a at week 0 and week 4. In three responders who had undetectable HCV RNA at week 28, endogenous IFN α -2a was found at the baseline but no exogenous IFN α -2a, but these three patients were not the same as the three patients with neutralizing antibody to IFN α -2a.

Discussion

The present study, which is the largest study examining unselected re-treated patients, showed no association between the response to a 12-week PEG IFN α -2a + RIBA session and neutralizing antibody to IFN α -2a. It was reported previously that if there is an association of the presence of neutralizing antibody to IFN α -2a and the absence of response to IFN α -2a, virological response may be restored or induced in hepatitis C-infected patients (patients who might develop an antibody-mediated resistance to conventional recombinant IFN treatment) [van der Eijk et al., 2006]. The study by Van der Eijk et al. (2006) did not describe the criteria for patient selection. In the present study only few non-responders had neutralizing antibodies to IFN α -2a. Thus the absence of neutralizing antibodies to IFN α -2a might not explain the absence of response.

A higher proportion of patients harboring neutralizing antibodies to IFN (39%) was found in the present study compared with the study by Leroy et al. [Leroy et al., 1998] (3 to 9%); but Leroy et al. (1998) did not find a relationship with initial response but rather with breakthrough.

It has been suggested recently that host genetics might be more useful for predicting drug response, as genome-wide association studies have reported associations between IL28B single polynucleotide polymorphisms and the response to antiviral treatment in individuals infected with HCV genotype 1. In these studies, eight single polynucleotide polymorphisms (rs8105790, rs12979860, rs11881222, rs8103142, rs28416813, rs4803219, rs8099917, and rs7248668) of IL28B were analyzed, with a view to identifying associations with the response to PEG IFN α -2a and RIBA [Ge et al., 2009; McCarthy et al.; Rauch et al., 2010; Suppiah et al., 2009; Thomas et al., 2009].

Isolated cases have been observed but might well be explained by a selection bias of very specific cases in single centers. Among re-treated patients, second-line treatment with PEG IFN α -2a + RIBA yields a virological response in the presence of antibody-mediated resistance to conventional IFN treatment, and neutralizing antibody to IFN α -2a cannot be considered as a predictor of a virological response among these patients. Nevertheless, there might be circumstances or populations behaving differently. Indeed,

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Jorns et al. [Jorns et al., 2006] showed that anti-IFN α -2a antibodies had already developed after the first of four unsuccessful IFN therapies, suggesting that neutralizing antibodies may have contributed to the failure of previous IFN treatment lines. However, would the results be the same if natural IFN were used for the second-line therapy instead of recombinant IFN? Indeed, there are several indications that neutralizing antibodies to recombinant IFN α do not redevelop during natural IFN re-treatment and, when still present, they are not able to neutralize all subtypes present in the mixture of natural IFN preparations [Antonelli et al., 1991; Antonelli et al., 1996; Berg et al., 2001; Milella et al., 1993; Milella et al., 1995; Roffi et al., 1995]. An association of neutralizing antibodies with treatment failure was reported previously [Basso et al., 2007; Cornberg et al., 2006; Poynard et al., 2009; Sherman et al., 2006; Shiffman, 2004; Taliani et al., 2006; Veldt et al., 2003]. Several studies showed that re-treatment with natural IFN was then able to restore or induce a virological response in hepatitis C patients who developed an antibody-mediated resistance to conventional recombinant IFN treatment [Antonelli et al., 1991; Antonelli et al., 1996]. In conclusion, this study shows that neutralizing antibodies to IFN α -2a can be found at similar levels in patients who respond and who do not respond to a re-treatment by PEG IFN α -2a + RIBA. Other mechanisms, such as host genetic or immunological factors, need to be identified and investigated in unbiased studies to explain most treatment failures among patients infected chronically by HCV and who adhered to their therapy.

References

- Antonelli G, Currenti M, Turriziani O, Dianzani F. 1991. Neutralizing antibodies to interferon-alpha: relative frequency in patients treated with different interferon preparations. *J Infect Dis* 163(4):882-885.
- Antonelli G, Giannelli G, Currenti M, Simeoni E, Del Vecchio S, Maggi F, Pistello M, Roffi L, Pastore G, Chemello L, Dianzani F. 1996. Antibodies to interferon (IFN) in hepatitis C patients relapsing while continuing recombinant IFN-alpha2 therapy. *Clin Exp Immunol* 104(3):384-387.
- Basso M, Torre F, Grasso A, Percario G, Azzola E, Artioli S, Bianchi S, Pelli N, Picciotto A. 2007. Pegylated interferon and ribavirin in re-treatment of responder-relapser HCV patients. *Dig Liver Dis* 39(1):47-51.
- Berg T, Hopf U, Schuff-Werner P. 2001. Sustained remission of chronic hepatitis C after a change to human leukocyte interferon-alpha in a difficult-to-treat patient with breakthrough phenomenon associated with antibodies against recombinant interferon-alpha. *Am J Gastroenterol* 96(2):612-614.
- Cornberg M, Hadem J, Herrmann E, Schuppert F, Schmidt HH, Reiser M, Marschal O, Steffen M, Manns MP, Wedemeyer H. 2006. Treatment with daily consensus interferon (CIFN) plus ribavirin in non-responder patients with chronic hepatitis C: a randomized open-label pilot study. *J Hepatol* 44(2):291-301.
- Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, Heinzen EL, Qiu P, Bertelsen AH, Muir AJ, Sulkowski M, McHutchison JG, Goldstein DB. 2009. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 461(7262):399-401.
- Hoofnagle JH. 2002. Course and outcome of hepatitis C. *Hepatology* 36(5 Suppl 1):S21-29.
- Jorns C, Holzinger D, Thimme R, Spangenberg HC, Weidmann M, Rasenack J, Blum HE, Haller O, Kochs G. 2006. Rapid and simple detection of IFN-neutralizing antibodies in chronic hepatitis C non-responsive to IFN-alpha. *J Med Virol* 78(1):74-82.
- Leroy V, Baud M, de Traversay C, Maynard-Muet M, Lebon P, Zarski JP. 1998. Role of anti-interferon antibodies in breakthrough occurrence during alpha 2a and 2b therapy in patients with chronic hepatitis C. *J Hepatol* 28(3):375-381.
- McCarthy JJ, Li JH, Thompson A, Suchindran S, Lao XQ, Patel K, Tillmann HL, Muir AJ, McHutchison JG. Replicated Association between an IL28B Gene Variant and a Sustained Response to Pegylated Interferon and Ribavirin. *Gastroenterology*.
- Micallef JM, Kaldor JM, Dore GJ. 2006. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat* 13(1):34-41.
- Milella M, Antonelli G, Santantonio T, Currenti M, Monno L, Mariano N, Angarano G, Dianzani F, Pastore G. 1993. Neutralizing antibodies to recombinant alpha-interferon and response to therapy in chronic hepatitis C virus infection. *Liver* 13(3):146-150.
- Milella M, Antonelli G, Santantonio T, Giannelli G, Currenti M, Monno L, Turriziani O, Pastore G, Dianzani F. 1995. Treatment with natural IFN of hepatitis C patients with or without antibodies to recombinant IFN. *Hepato-gastroenterology* 42(3):201-204.
- Poynard T, Colombo M, Bruix J, Schiff E, Terg R, Flamm S, Moreno-Otero R, Carrilho F, Schmidt W, Berg T, McGarrity T, Heathcote EJ, Goncalves F, Diago M, Craxi A, Silva M, Bedossa P, Mukhopadhyay P, Griffel L, Burroughs M, Brass C, Albrecht J. 2009. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. *Gastroenterology* 136(5):1618-1628 e1612.

Rauch A, Kutalik Z, Descombes P, Cai T, Di Iulio J, Mueller T, Bochud M, Battegay M, Bernasconi E, Borovicka J, Colombo S, Cerny A, Dufour JF, Furrer H, Gunthard HF, Heim M, Hirschel B, Malinverni R, Moradpour D, Mullhaupt B, Witteck A, Beckmann JS, Berg T, Bergmann S, Negro F, Telenti A, Bochud PY. 2010. Genetic Variation in IL28B Is Associated With Chronic Hepatitis C and Treatment Failure: A Genome-wide Association Study. *Gastroenterology*.

Roffi L, Mels GC, Antonelli G, Bellati G, Panizzuti F, Piperno A, Pozzi M, Ravizza D, Angeli G, Dianzani F, et al. 1995. Breakthrough during recombinant interferon alfa therapy in patients with chronic hepatitis C virus infection: prevalence, etiology, and management. *Hepatology* 21(3):645-649.

Seeff LB. 2002. Natural history of chronic hepatitis C. *Hepatology* 36(5 Suppl 1):S35-46.

Sherman M, Yoshida EM, Deschenes M, Krajden M, Bain VG, Peltekian K, Anderson F, Kaita K, Simonyi S, Balshaw R, Lee SS. 2006. Peginterferon alfa-2a (40KD) plus ribavirin in chronic hepatitis C patients who failed previous interferon therapy. *Gut* 55(11):1631-1638.

Shiffman ML. 2004. Management of patients with chronic hepatitis C virus infection and previous nonresponse. *Rev Gastroenterol Disord* 4 Suppl 1:S22-30.

Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore GJ, Powell E, Riordan S, Sheridan D, Smedile A, Fragomeli V, Muller T, Bahlo M, Stewart GJ, Booth DR, George J. 2009. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 41(10):1100-1104.

Taliani G, Gemignani G, Ferrari C, Aceti A, Bartolozzi D, Blanc PL, Capanni M, Esperti F, Forte P, Guadagnino V, Mari T, Marino N, Milani S, Pasquazzi C, Rosina F, Tacconi D, Toti M, Zignego AL, Messerini L, Stroffolini T. 2006. Pegylated interferon alfa-2b plus ribavirin in the retreatment of interferon-ribavirin nonresponder patients. *Gastroenterology* 130(4):1098-1106.

Thomas DL, Seeff LB. 2005. Natural history of hepatitis C. *Clinical Liver Diseases* 9:383-398.

Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, Kidd J, Kidd K, Khakoo SI, Alexander G, Goedert JJ, Kirk GD, Donfield SM, Rosen HR, Tobler LH, Busch MP, McHutchison JG, Goldstein DB, Carrington M. 2009. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 461(7265):798-801.

van der Eijk AA, Vrolijk JM, Haagmans BL. 2006. Antibodies neutralizing peginterferon alfa during retreatment of hepatitis C. *N Engl J Med* 354(12):1323-1324.

Veldt BJ, Brouwer JT, Adler M, Nevens F, Michielsens P, Delwaide J, Hansen BE, Schalm SW. 2003. Retreatment of hepatitis C non-responsive to interferon. A placebo controlled randomized trial of ribavirin monotherapy versus combination therapy with Ribavirin and Interferon in 121 patients in the Benelux [ISRCTN53821378]. *BMC Gastroenterol* 3:24.

WHO. 2000. Hepatitis C. Fact Sheet No. 164.

Appendix

Financial Support:

This study was sponsored by ANRS (French National Agency For Research on Aids and Viral hepatitis). Roche kindly provided Pegylated-Interferon, and Ribavirine and InterMune, Inc. kindly provided Interferon γ -1b.

ANRS HC16 GAMMATRI study group:

Investigator Site:

Saint Joseph hospital, Marseille: M. Bourlière, V. Oules; **Haut Lévêque hospital, Pessac:** P. Couzigou, J. Foucher, L. Castéra, P. Trimoulet, J. Berthet, N. Le Provost; **Brabois hospital, Vandoeuvre Les Nancy:** J.P. Bronowicki, L. Chone, L. Arowas, S. Khaled-Jousselin; **Pitié-Salpêtrière hospital, Paris:** Th. Poynard, Y. Benhammou, V. Ratziu, C. Blot; **Albert Michallon hospital, Grenoble:** J.P. Zarski, V. Leroy, A. Plagès; **Beaujon hospital, Clichy:** P. Marcellin, T. Asselah; **Saint André hospital, Bordeaux:** C. Balabaud, P.H. Bernard, J. Foucher.

Steering Committee: L. Allain, P.H. Bernard, M. Bourlière, J.P. Bronowicki, G. Chêne, P. Couzigou, V. Leroy, P. Marcellin, S. Pérusat, P. Trimoulet, J.P. Zarski.

Clinical Trials Unit/INSERM U897, Bordeaux School of Public Health (ISPED), University Victor Segalen Bordeaux 2: A. André, V. Boilet, G. Chêne, S. Pérusat.

Sponsor, ANRS: L. Allain, A. Metro, C. Paul, N. Squalli

Table 1: Endogenous IFN- α , presence of neutralizing antibody to IFN- α , and treatment response at week 12; analysis of 42 patients of the ANRS HC16 GAMMATRI trial

		HCV RNA decrease > 2log ₁₀ at week 12				
		yes		no		
		(responders)		(non-responders)		
Neutralizing antibody to IFN-α						
Week 0						
	> 1.38 ng/ml (%)	3	(16)	5	(22)	p=0.700
	Median (IQR*)	0	(0-0)	0	(0-0)	
Week 4						
	> 1.38 ng/ml (%)	6	(32)	6	(26)	p=1.000
	Median (IQR*)	0	(0-53)	0	(0-81)	
Week 12						
	> 1.38 ng/ml (%)	7	(37)	6	(26)	p=0.057
	Median (IQR*)	0	(0-124)	0	(0-33)	
Interferon α-2a levels						
Week 0						
	> 3.3 pg/ml (%)	4	(21)	12	(52)	p=0.057
	Median (IQR*)	0	(0-0)	85	(0-181)	
Week 4						
	> 3.3 pg/ml (%)	18	(95)	21	(91)	
	Median (IQR*)	1457	(876-1722)	1407	(960-1903)	
Week 12						
	> 3.3 pg/ml (%)	19	(100)	22	(96)	
	Median (IQR*)	1652	(1147-2633)	1620	(1297-1785)	

Abbreviation: IQR = interquartile range