Education by a Nurse Increases Response of Patients With Chronic Hepatitis C to Therapy With Peginterferon-α2a and Ribavirin

DOMINIQUE LARREY,* ANNIE SALSE,* DIDIER RIBARD,† OLIVIER BOUTET,† VALÉRIE HYRAILLES-BLANCO,‡ BIRAME NIANG,§ GEORGES PHILIPPE PAGEAUX,* EMMANUEL VAUCHER,** JEAN PIERRE ARPURT,†† GUY BOULAY,§§ NATALIA KARLOVA,|| JEAN PIERRE DAURES,||| and the Hepatitis C Network of Languedoc Roussillon (France)

*Hepato-Gastroenterology, Saint Eloi Hospital, Montpellier; †INSERM U632, Montpellier; ‡Hepato-Gastroenterology, Caremeau Hospital, Nimes; §Hepato-Gastroenterology, Bagnols/Ceze Hospital, Bagnols/Ceze; ¶Hepato-Gastroenterology, Beziers Hospital, Beziers; ††Hepato-Gastroenterology, Ales Hospital, Ales; ||Hepato-Gastroenterology, Narbonne Hospital, Narbonne; |||Hepato-Gastroenterology, Arles Hospital, Arles; and §§Laboratory Roche, Paris; and the ¶¶Biostatistics Department, Institut Universitaire de Recherche Clinique, Montpellier, France

BACKGROUND & AIMS: Education of patients with chronic hepatitis C has been proposed to increase response to therapy with peginterferon and ribavirin. We performed a prospective study to determine the effects of systematic consultation by a nurse on patient adherence and the efficacy of therapy.

METHODS: We analyzed data from 244 patients who received either systematic consultation after each medical visit from a nurse who used a standard evaluation grid and provided information about the disease and treatment (group A [GrA], n = 123) or the conventional clinical follow-up procedure (group B [GrB], n = 121). Treatment lasted 24 to 48 weeks.

RESULTS: Characteristics of each group were similar at baseline, including prior treatment (42.6% in GrA and 36.0% in GrB). Overall, GrA had significantly better adherence to treatment than GrB (74.0% vs 62.8%), especially among patients who received 48 weeks of treatment (69.7% vs 53.2%; P < .03). Significantly more patients in GrA had a sustained virologic response, compared with GrB overall (38.2% vs 24.8%; P < .02), as well as treatment-naive patients (47.1% vs 30.3%; P < .05), and those with genotypes 1, 4, or 5 infections (31.6% vs 13.3%; P < .007). There were no differences between GrA and GrB in response of patients with genotypes 2 or 3 infections or advanced fibrosis. Prognostic factors for a sustained virologic response (based on bivariate and multivariate analyses) were virologic response at week 12 (odds ratio [OR], 1.9; P < .001), genotypes 2 or 3 (OR, 2.9; P < .001), therapeutic education (OR, 2.5; P < .02), and lack of previous treatment (OR, 2.3; P < .005).

CONCLUSIONS: Therapeutic education by a specialized nurse increases the response of patients with hepatitis C to therapy, particularly in difficult-to-treat patients.

Keywords: HCV; Prognosis; Virus; Clinical Trial; Liver Disease.

**Hepato-Gastroenterology, Narbonne Hospital, Narbonne; ‡‡Hepato-Gastroenterology, Avignon Hospital, Avignon; §§Hepato-Gastroenterology, Arles Hospital, Arles; and ¶¶Laboratory Roche, Paris; and the ¶¶Biostatistics Department, Institut Universitaire de Recherche Clinique, Montpellier, France

The treatment of chronic hepatitis C (CHC) based on the combination of peginterferon-α2a or -2b and ribavirin is associated with a sustained virologic response (SVR) of slightly more than 50% of patients, with variations depending on genotype (genotypes 1–4).

Poor adherence is one of the major factors of therapeutic failure.1–7 This may be owing to unfavorable treatment conditions such as chronic alcoholism, obesity, insulin resistance, and poor social conditions, but especially to the reduction of optimal doses or duration of treatment.1–7 One of the main reasons for dose reducing is the side effects of treatment.1–7 The decrease in adherence is found in most chronic diseases requiring long-term treatment.8 As a result, the notion of therapeutic education and patient counseling has been developed for numerous chronic diseases, in particular the human immunodeficiency virus, diabetes, cardiovascular diseases, and rheumatic diseases.9–11 By analogy, this has prompted recommendations to improve the management of treatment by placing the patient in the center of an organization that includes social service professionals and medical personnel.5 However, the efficacy of ideal global patient management has not been proven scientifically. We performed this prospective study to evaluate the influence of systematic management of the patient and his/her family by a nurse with combination therapy for CHC (PegInferon Observance study).

The main aim of this study was to determine the influence of systematic consultations with a nurse on adherence to treatment associating peginterferon-α2a and ribavirin in CHC and on the virologic response.

The secondary aims included the following: (1) defining the reasons and behaviors associated with poor adherence; (2) determining the prognostic factors of achieving an SVR; (3) measuring the impact of these consultations on the patient’s quality of life; and (4) evaluating the medico-economic impact of this approach. The results of the 2 latter aims are the object of a separate article and are not included in this article.

Patients and Methods

This was a randomized, comparative, multicentric, prospective clinical study coordinated by the Montpellier School of Medicine Liver Unit (center 1) with the Hepatitis Network of Languedoc-Roussillon, France (Supplementary Appendix 1). This study was approved by the Committee for the Protection of Individuals of the Montpellier-Nimes School of Medicine. Patients were allocated to 2 parallel groups by open-label ran-

**Abbreviations used in this paper: CHC, chronic hepatitis C; EVR, early virologic response; GrA, group A; GrB, group B; OR, odds ratio; SVR, sustained virologic response.**

© 2011 by the AGA Institute

1542-3565/$36.00
doi:10.1016/j.cgh.2011.05.022
domination (1:1): group A (GrA), including systematic stan-
standardized consultation with a nurse; and group B (GrB) includ-
ing conventional clinical follow-up evaluation.

Patients
Adult patients (≥18 y) with documented genotype 1
CHC, without human immunodeficiency virus and hepatitis B
virus co-infection, with an indication for peginterferon-α2a-
ribavirin treatment, who provided written consent to partici-
pate in the study were eligible (inclusion and exclusion criteria
are detailed fully in the Supplementary Materials and Methods).
Patients could be treatment-naive or treatment-experienced (vi-
rologic nonresponders or relapser after treatment).

Treatment Regimen
The treatment included peginterferon-α2a, 180 μg/wk, subcutaneously, independent of body weight, and ribavirin with
oral twice-daily dosing depending on body weight (<75 kg, 1000 mg/d; >75 kg, 1200 mg/d), for 24 or 48 weeks depending
on the genotype, viral load, and possible previous treatment.

Follow-up Protocol
GrA patients were followed up during scheduled visits,
with a medical consultation by the investigating physician
(Supplementary Materials and Methods) followed by a consul-
tation with a nurse for scheduled evaluations. These visits were
systematic at the beginning of treatment day 0, week 4, week 8,
week 12, week 24, and in patients with 48 weeks of treatment at
week 36.

GrB patients were followed up during scheduled visits
with a medical consultation by the investigating physician but with-
out systematic consultation with the nurse, thus they received
conventional clinical follow-up evaluation.

SVR was evaluated at 12 and 24 weeks after the end of
treatment.

Methodologic Protocol for Consultation With the Nurse
The nurse’s goals were to evaluate the patient’s under-
standing of the disease and side effects of treatment, and to
improve adherence to treatment. The progress of the consulta-
tion with the nurse and the questionnaires (Supplementary
Appendix 2) used as tools to meet the 2 goals are described
extensively in the Supplementary materials.

Statistical Methods
Sample size. When the study was organized, the per-
centage of adherence to treatment at 24 weeks in the standard
follow-up group based on an analysis of the literature was
evaluated at 60%. A 15% increase in adherence with therapeutic
education, or 75% adherence in the group receiving systematic
therapeutic education from a nurse, was hypothesized based on
open-label studies. To illustrate this difference, with a risk of a
type I error of 5% (unilateral test), a power of 90%, and a
potential 10% of patients lost to follow-up evaluation, the
number of patients that was needed was 184 per group, or a
total of 368 patients.

Data were processed with SAS software (SAS Institute, Cary,
NC). Because the analysis was randomized, analysis of variance
or the Wilcoxon test was used to compare quantitative and
qualitative variables (at entry), and qualitative variables were
analyzed with the χ² test or the Fisher test. Variables with a P
value less than .15 were selected for multivariate logistic regres-
sion analysis, which was performed to identify prognostic fac-
tors of SVR.

The analysis was performed on an intention-to-treat basis. A
P value of .05 was considered significant.

Results
A total of 250 patients were randomized, including 6
patients who refused treatment in GrB. The analysis therefore
was based on 244 patients, with 123 patients in GrA and 121
patients in GrB. Center 1 recruited 128 patients (Supplemen-
tary Figure 1).

Table 1 shows the main baseline patient characteristics that
were similar in both groups. There were no differences between
the groups for alcohol consumption, delay between infection
and date of diagnosis (14.2 vs 15.2 y), the route of transmission,
and frequency of treatment-naive or re-treatment patients.

Table 2 shows the adherence to treatment according to the
planned duration of treatment. Adherence to treatment for all
patients tended to be better in the therapeutic education group.
This tendency increased along treatment duration and was near
significant (P = .06) at treatment end (GrA 74% vs GrB 62.8%).
There was no difference in adherence between the 2 groups in
patients with 24-week treatment. In patients with 48-week

| Table 1. Baseline Characteristics of Patients With CHC |
| --- | --- | --- |
| Mean age (±SD), y | GrA (n = 123) | GrB (n = 121) | P value |
| Male sex, n (%) | 79 (64.2) | 74 (61.1) | NS |
| Mean BMI (±SD), kg/m² | 23.9 (3.5) | 24.5 (4.4) | NS |
| Mean serum ALT level (±SD) | 2.0 ULN (1.9) | 1.9 ULN (1.2) | NS |
| Median serum HCV level RNA level (±SD) | 2310⁶ IU/mL (6 × 10⁶) | 1110⁶ IU/mL (1 × 10⁶) | NS |
| Genotype 1 (%) | 70 (56.9) | 64 (52.8) | NS |
| Genotypes 2/3 (%) | 44 (35.8) | 46 (38) | NS |
| Moderate fibrosis F0–F2 (%)² | 88 (70.6) | 86 (77.9) | NS |
| Extensive fibrosis/cirrhosis F3–F4 (%)² | 35 (29.4) | 35 (32.1) | NS |
| Treatment naive (%) | 70 (57.4) | 76 (63.9) | NS |
| Previous treatment (%) | 53 (42.6) | 45 (36.1) | NS |

ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus; ULN, number of times the upper limit of normal.
²Fibrosis level expressed according to METAVIR scale.12,15,16
Table 2. Adherence to Treatment According to Initially Planned Duration

<table>
<thead>
<tr>
<th></th>
<th>GrA</th>
<th>GrB</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treatments (24 and 48 wk)</td>
<td>244 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence at 12 wk</td>
<td>100 (81.3%)</td>
<td>92 (74.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Adherence at 24 wk</td>
<td>93 (75.6%)</td>
<td>80 (66.1%)</td>
<td>.1</td>
</tr>
<tr>
<td>Adherence for complete treatment (24 or 48 wk)</td>
<td>91 (74.0%)</td>
<td>76 (62.8%)</td>
<td>.06</td>
</tr>
<tr>
<td>Treatment planned for 24 wk</td>
<td>80 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence at 12 wk</td>
<td>32 (86.5%)</td>
<td>38 (88.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Adherence for complete treatment</td>
<td>31 (83.6%)</td>
<td>35 (76.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment planned for 48 wk</td>
<td>164 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence at 12 wk</td>
<td>68 (79%)</td>
<td>54 (70%)</td>
<td>NS</td>
</tr>
<tr>
<td>Adherence at 24 wk</td>
<td>62 (72.1%)</td>
<td>44 (57.1%)</td>
<td>.04</td>
</tr>
<tr>
<td>Adherence for complete treatment</td>
<td>60 (69.7%)</td>
<td>41 (53.2%)</td>
<td>.03</td>
</tr>
</tbody>
</table>

NOTE. Adherence has been defined as the continuation of treatment as normally scheduled. Patients with early discontinuation were classified as nonadherent.

Table 4 and Supplementary Table 1 show virologic response results. For all patients, serum HCV RNA level was undetectable (detection threshold, 50 UI/L) in more patients in GrA than in GrB at week 12 (72.8% vs 57.6%, respectively), at week 24 (75.2% vs 60.7%), at the end of treatment (70.6% vs 53.4%, respectively), and 24 weeks after the end of treatment (with an SVR of 38.2% vs 24.8%, respectively) (Table 4).

The influence of therapeutic education varied according to the planned duration of treatment. Indeed, for a 24-week treatment there was no difference in virologic response at week 12, at the end of treatment, or 24 weeks after treatment.

For a 48-week treatment, the virologic response was better in GrA at weeks 12 and 24, at the end of treatment, and 24 weeks after treatment.

Supplementary Table 1 shows the SVR according to the 3 main baseline parameters: absence of previous treatment or previous treatment (24 or 48 wk), and 24 Weeks After Treatment (Viral Load < 50 IU/L).

NOTE. Several causes were associated in the same patient.

Table 3. Early Discontinuation of Treatment: Frequency and Causes

<table>
<thead>
<tr>
<th></th>
<th>GrA (n = 123)</th>
<th>GrB (n = 121)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number and frequency</td>
<td>32 (26.0%)</td>
<td>45 (37.0%)</td>
<td>.06</td>
</tr>
<tr>
<td>Treatment side effects</td>
<td>9 (7.3%)</td>
<td>13 (10.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Associated disease</td>
<td>3 (2.5%)</td>
<td>6 (4.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Patient’s decision/poor adherence</td>
<td>10 (8.9%)</td>
<td>14 (11.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>No virologic response</td>
<td>4 (3.2%)</td>
<td>10 (8.2%)</td>
<td>.09</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>3 (2.4%)</td>
<td>2 (1.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Lost to follow-up evaluation</td>
<td>1 (0.8%)</td>
<td>4 (3.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Other causes</td>
<td>4 (3.2%)</td>
<td>2 (1.6%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE. Adherence at 24 wk 55 (66.2%) 32 (42.7%) .006
| Week 24 post-treatment       | 26 (30.2%)   | 10 (13.0%)   | .008    |

In previously treated patients, the overall SVR was 2 times lower than in treatment-naive patients, in both GrA and GrB. Nevertheless, in GrA the SVR tended to be higher than in GrB but without being significant because of the low number of patients.

According to Genotype

SVR was significantly higher for genotypes 1, 4, 5, and 6 in GrA than in GrB in all patients (treatment naive and previously treated patients) at 31.7% versus 13.3%, respectively (P < .007).

For genotypes 2 and 3, whose overall SVR results were higher in both groups (A or B), there was no significant difference between groups A and B (50.0% vs 43.5%, respectively).

Impact of Fibrosis

SVR for the entire study group was slightly higher in patients with moderate fibrosis (F2 or less) in GrA than in GrB (36.9% vs 28.4%, respectively), but this difference was not significant. In patients with advanced fibrosis or cirrhosis (F3, F4), SVR was higher in GrA than in GrB (42.8% vs 17.0%, respectively) (P < .01).

Analysis of Prognostic Factors of SVR

Supplementary Table 2 shows the results of bivariate analysis. The following were found to be significant prognostic factors of SVR: therapeutic education in GrA, initial treatment, genotype 2 or 3 infection, and an early virologic response (EVR) with undetectable serum HCV RNA level at week 12 of treatment.

The following parameters were not significant: advanced fibrosis, male sex, baseline viral load of less than 715,000 UI and alanine aminotransferase activity, sex, age younger than 45 years, and management in center 1.

Table 5 shows a multivariate analysis of the probability of achieving an SVR. Genotypes 2/3 were found with an odds ratio (OR) of 2.9, being treated in GrA with therapeutic education (OR, 1.5), being a treatment-naive patient (OR, 2.3), a baseline viral load of less than 715,000 UI (OR, 1.8), or treatment in center 1 (OR, 1.8).
follow-up group (Table 4). The SVR increased by more than 50%, independent of the treatment duration and genotype (Table 4). This difference was found mainly in patients with 48 weeks of treatment, but was not significant in those with 24 weeks of treatment.

The lower SVR rate compared with pivotal trials can be explained by several factors, as follows: (1) the presence of nonresponder patients; (2) less strict patient selection than in therapeutic trials in which the goal is to obtain marketing approval; and (3) inclusion of patients who are similar to those found in actual clinical practice.

Therapeutic education had a significant beneficial effect on several factors known to influence SVR rate: treatment-naive status, difficult-to-treat genotypes 1, 4, 5, and 6, and advanced fibrosis. There was also a tendency to a better, but not significant, response in nonresponder and relapser patients being re-treated, whatever the genotype. On the other hand, there was no significant difference in patients with genotypes 2 and 3 whether they were treatment-naive or had been treated previously, or in patients with moderate fibrosis (Supplementary Table 1).

The bivariate analysis identified the following prognostic factors for achieving an SVR (Supplementary Table 2): initial treatment in naive patients, genotypes 2 and 3, or EVR as in previous pivotal studies. Therapeutic education was an additional significant prognostic factor. By multivariate analysis (Table 5), the following prognostic factor was found to be significant: genotypes 2 and 3 and initial treatment in naive patients as in pivotal studies. Therapeutic education was another important prognostic factor with an OR of 2.5 (range, 1.3–4.6). After adjustment for EVR, the factors with positive prognostic value were initial treatment in treatment-naive patients (OR, 2.4; range, 1.1–4.8) and therapeutic education group (OR, 2.3; range, 1.1–4.6). Genotypes 2 and 3 had no significant value. The results of bivariate and multivariate analysis for prognostic factors suggests the following comments.

Because half the patients were recruited from the organizing center (center 1), there was a question of whether there was a center effect in the results. Bivariate and multivariate analyses did not show center 1 to have a prognostic value for achieving an SVR, showing no significant center effect on overall results. Bivariate and multivariate analyses showed EVR as an SVR prognostic factor. This suggests that the beneficial effect of therapeutic education is especially important during the first 3 months of treatment.

Two other prospective studies focused on therapeutic education in patients with CHC treatment have been performed recently with different methodologies. One was a cohort study without standardization of therapeutic education. The adherence and SVR were found to be specifically better per-protocol in patients with genotypes 2/3. The absence of intent-to-treat analysis may explain the difference with our study. Results for the other genotypes, in particular genotypes 1 and 4, have not yet been published.

Another nonrandomized study recently compared the influence of a nurse associated with a hepatologist with a standard care. There was no methodologic planning for consultations with a nurse. The results, recently published in abstract form, showed an overall improvement in adherence and SVR independent of the genotype as in our study.

### Discussion

This was a randomized prospective study to confirm the positive impact of a standardized predefined method of therapeutic education on adherence and an SVR.

Among the 250 randomized patients, the 6 who withdrew their consent to participate in the study and did not receive treatment had been randomized into the group without therapeutic education. Withdrawal from the study may have been related to the expectation of a potential benefit from the nurse care. Half of the patients were recruited from center 1; therefore, a center effect was evaluated.

The number of patients included in this study was lower than the initially calculated number: 244 instead of 368. Indeed, after the intermediate-term results of this study, most centers refused to continue including patients with a 50% probability to be in the group without systematic therapeutic education. Nevertheless, the results were significant and the power reached with the existing sample was sufficient.

Patient demographic characteristics were similar between the groups and comparable with those of other studies.

The first study aim was to determine adherence to treatment. Adherence for the entire treatment period was 62.8% in the standard clinical follow-up group, which is comparable with that in actual clinical conditions and for other chronic diseases. Therapeutic education tended to improve treatment adherence in the entire group without reaching significance. The results varied according to the planned treatment duration. It had no benefit in the shortest 24-week treatment, whereas it was significantly better in the longest 48-week treatment (Table 2).

The main reasons for treatment discontinuation were undesirable side effects, the patient’s decision, and lack of virologic response, particularly in treatment-experienced patients (Table 3).

For all treatments, virologic response was better in the therapeutic education group compared with the standard clinical

### Table 5: SVR: Multivariate Analysis of Prognostic Factors

<table>
<thead>
<tr>
<th>Model showing the probability of having an SVR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypes 2/3</td>
<td>2.9 (1.5–5.4)</td>
</tr>
<tr>
<td>Group A</td>
<td>2.5 (1.3–4.6)</td>
</tr>
<tr>
<td>Naive patients</td>
<td>2.3 (1.2–0.5)</td>
</tr>
<tr>
<td>Serum HCV RNA level, &lt;715,000 IU/L</td>
<td>1.8 (0.99–3.3)</td>
</tr>
<tr>
<td>Center 1</td>
<td>1.8 (0.98–3.4)</td>
</tr>
</tbody>
</table>

Model showing the probability of having an SVR integrating undetectable serum HCV RNA level at week 12

<table>
<thead>
<tr>
<th>Serum HCV RNA level undetectable at week 12</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive patients</td>
<td>2.4 (1.1–4.8)</td>
</tr>
<tr>
<td>Group A</td>
<td>2.3 (1.1–4.6)</td>
</tr>
<tr>
<td>Genotypes 2/3</td>
<td>1.9 (0.96–3.8)</td>
</tr>
</tbody>
</table>

NOTE. This cut-off level has been determined according to the median of serum HCV viral load in the total number of patients in the study.

The probability of achieving an SVR also was determined, taking into account EVR (Table 5). Results show treatment-naive patients (OR, 2.4) being treated in GrA with therapeutic education (OR, 2.3) and genotypes 2/3 (OR, 1.9).

The results of bivariate and multivariate analysis for prognostic factors suggest the following comments.

Because half the patients were recruited from the organizing center (center 1), there was a question of whether there was a center effect in the results. Bivariate and multivariate analyses did not show center 1 to have a prognostic value for achieving an SVR, showing no significant center effect on overall results. Bivariate and multivariate analyses showed EVR as an SVR prognostic factor. This suggests that the beneficial effect of therapeutic education is especially important during the first 3 months of treatment.

Two other prospective studies focused on therapeutic education in patients with CHC treatment have been performed recently with different methodologies. One was a cohort study without standardization of therapeutic education. The adherence and SVR were found to be specifically better per-protocol in patients with genotypes 2/3. The absence of intent-to-treat analysis may explain the difference with our study. Results for the other genotypes, in particular genotypes 1 and 4, have not yet been published.

Another nonrandomized study recently compared the influence of a nurse associated with a hepatologist with a standard care. There was no methodologic planning for consultations with a nurse. The results, recently published in abstract form, showed an overall improvement in adherence and SVR independent of the genotype as in our study.
The limitations of this study were the relatively low number of participating patients and the choice to centralize therapeutic education only to specialized nurse care. Other methods also probably would be beneficial. Multidisciplinary protocols probably would improve results even more. These avenues must be explored in controlled studies to validate the notion of multidisciplinary management.

In conclusion, this study showed the importance of therapeutic education in the management of CHC with peginterferon-ribavirin by resulting in better adherence to treatment and more cases of an SVR, particularly in the most difficult to treat patients.

**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org and doi:10.1016/j.cgh.2011.05.022.

**References**


5. Larrey D. [Chronic hepatitis C: apart from antiviral treatment what other measures should be recommended?]. Gastroenterol Clin Biol 2002;26:B283–B290.


Reprint requests

Address requests for reprints to: Dominique Larrey, MD, PhD, Département d’Hépato-Gastroentérologie et Transplantation, Hôpital Saint Eloi, 80 Rue Augustin Fliche, 34295 Montpellier Cedex 5, France. e-mail: dom-larrey@chu-montpellier.fr; fax: (00-33) 0-4-67-33-02-57.

Conflicts of interest

This author discloses the following: Natalia Karlova is employed by Roche Laboratory. The remaining authors disclose no conflicts.

Funding

Supported by the Association pour l’Etude des Maladies de l’Appareil Digestif; and by a grant from Roche Laboratory supporting the logistical management of the study (D.L.)