Prophylactic Treatment With Escitalopram of Pegylated Interferon Alfa-2a–Induced Depression in Hepatitis C: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Depression is one of the main reasons for treatment withdrawal and failure in chronic hepatitis C patients treated with interferon. Antidepressants are useful for its treatment, but whether they can also be used for prevention has yet to be established.

Method: To evaluate the efficacy and safety of escitalopram for preventing interferon alfa-2a–induced depression, we conducted an investigator-initiated multicenter, randomized, double-blind, placebo-controlled trial in 133 chronic hepatitis C patients without baseline mental disorders who were randomly assigned to receive escitalopram or placebo during the first 12 weeks of treatment. Primary efficacy outcomes were the development of *DSM-IV* major depression and scores on the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hospital Anxiety and Depression Scale (HADS). Primary safety end points were biochemical and virological responses. Patients were recruited between March 2005 and July 2006.

Results: Rates of major depression were low (5.4%) and did not differ between placebo (3.2%) and escitalopram (7.6%). MADRS and HADS scores significantly increased during treatment ($P < .001$ and $P = .028$, respectively), but there were no differences between treatment groups. Sustained virological response was achieved by 69.2% of patients, 70.4% in the placebo group and 67.9% in the escitalopram group.

Conclusions: Findings do not support the use of an antidepressant to prevent interferon-induced depression during the first 12 weeks of treatment in chronic hepatitis C patients at low psychiatric risk. Future studies should be directed to subpopulations of patients at high psychiatric risk.

Trial Registration: clinicaltrials.gov Identifier: NCT00166296

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Treatment of chronic hepatitis C (CHC) with interferon alfa is associated with a high incidence of depressive symptoms.[1–4] These adverse effects are one of the main reasons for treatment discontinuation, dose reductions, and noncompliance,[5–7] all of which can contribute to treatment failure.[8] Depressive symptoms are also a major reason for excluding CHC patients from potentially curative antiviral therapy.[9–11]

Several open studies and case reports,[12,13] as well as 1 randomized double-blind trial,[14] showed that antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), are useful in treating interferon-induced depression. Another strategy, a prophylactic one, has also been proposed: to pretreat patients with antidepressants for preventing the appearance of depressive symptoms during interferon and ribavirin therapy. This approach was supported by the publication of a double-blind, randomized trial showing that pretreatment with paroxetine, an SSRI, reduced the incidence of major depression in patients receiving high-dose interferon alfa for malignant melanoma.[15] In CHC patients, several open trials showed similar results,[16] especially in psychiatric risk patients.[17–19] However, the use of antidepressants in patients who currently do not have depression remains controversial, given concerns about polypharmacy and potential liver toxicity or additional side effects. Moreover, the influence of interferon-induced depressive symptoms and the use of antidepressants on the likelihood of viral response is also unclear.[20–22]

To our knowledge, only 2 randomized controlled studies have been published to date, showing that paroxetine, an SSRI antidepressant, cannot prevent interferon-induced depressive episodes but can improve depression severity, especially in patients with higher depression measures at baseline.[23,24] However, samples were small. Furthermore, other antidepressants should be tested.

Accordingly, we attempted to evaluate, in a double-blind, randomized trial, whether pretreatment with escitalopram, another SSRI, can prevent major depression in CHC patients receiving pegylated interferon alfa-2a and ribavirin. We also tried to assess the safety of the antidepressant and its relationship to viral response. This was an investigator-initiated, Spanish multicenter trial.

METHOD

Patients

Participants were recruited among CHC patients between 18 and 65 years old, referred by general practitioners between March 2005 and July 2006 to gastroenterology outpatient units in 15 academic general hospitals in Spain, who were suitable to initiate treatment with pegylated interferon

alfa-2a and ribavirin. Diagnosis of CHC was made by (1) at least 6 months of persistent elevated serum alanine aminotransferase (ALT), (2) detection of serum antihepatitis C virus (HCV) antibodies, and (3) detectable levels of serum HCV RNA using a polymerase chain reaction.

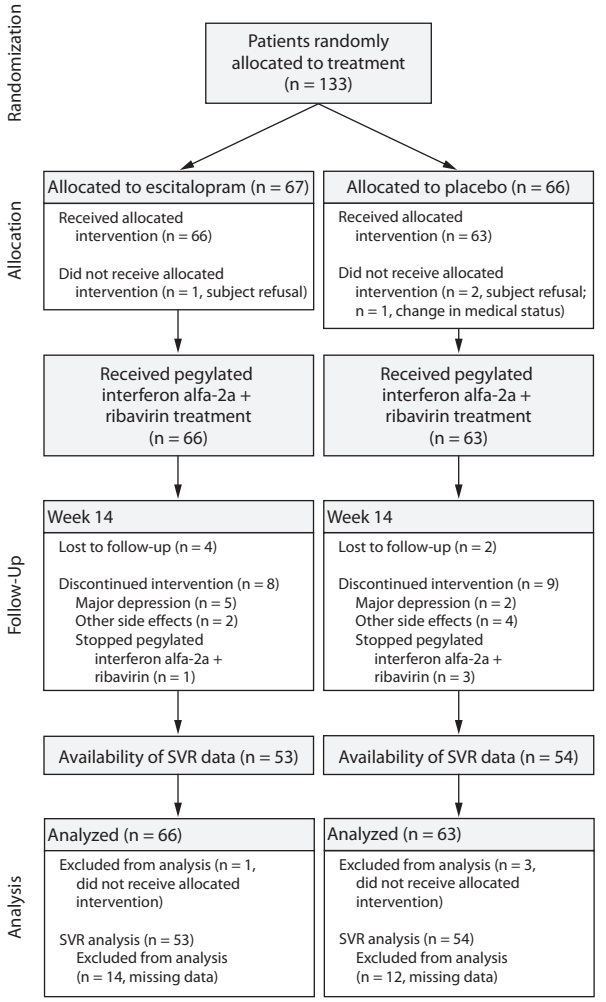
The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and posterior amendments, and it had been previously approved by the ethics committees of all centers involved and by the Spanish Agency of Medicines. All patients signed a written informed consent statement before entering the study. This study was registered at clinicaltrials.gov (NCT00166296).

General exclusion criteria included decompensated cirrhosis or hepatocellular carcinoma; liver disease of any cause other than HCV; unstable cardiovascular, endocrinologic, hematologic, renal, autoimmune, or neurologic disease; coinfection with hepatitis B virus or human immunodeficiency virus (HIV); a neutrophil count < 1500 or a platelet count < 70,000 per μL; hemoglobin < 12 g/dL in men and < 11 g/dL in women; nonreliable contraception in women; and insufficient knowledge of the Spanish language.

Psychiatric exclusion criteria were a past history of or current diagnoses of schizophrenia, bipolar disorder, or dementia; and the presence, within 2 months of study entry, of drug or alcohol abuse, symptomatic mental disorders (including major depressive disorder, dysthymia, and anxiety disorders other than specific phobias), and the use of any psychiatric medication (patients were only allowed to maintain treatments with benzodiazepines at constant dosages). Zolpidem was used for insomnia when needed.

All psychiatric diagnoses were made by senior psychiatrists applying the lifetime Structured Clinical Interview for *DSM-IV* Axis I Disorders, Research Version, Nonpatient Edition (SCID-I/NP),[25] which follows criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*).[26]

Figure 1. Study Flow Diagram



Abbreviation: SVR = sustained virological response.

Procedures

Sample size calculations were based on data from the antidepressant trial in melanoma patients, in which 45% of placebo-treated patients developed major depression during interferon alfa therapy compared with 11% of paroxetine-treated subjects.[15] A sample size of 100 would give a 0.95 power to detect significant differences in major depression between groups ($P = .05$, 2-sided). We also used data from 2 studies using Montgomery-Asberg Depression Rating Scale (MADRS) scores in CHC patients.[27,28] In this case, a sample size of 112 would give a 0.80 power to detect differences of 5.0 points in MADRS scores ($P = .05$, 2-sided) assuming an SD of 9.3. We planned to enroll a total of 130 patients to compensate for dropouts.

Of 133 patients finally randomized, 67 were allocated to receive escitalopram, and 66 received placebo (Figure 1). Escitalopram and placebo pills were supplied by H. Lundbeck A/S and were identical in shape, size, and color. The gastroenterologists responsible for seeing the patients allocated them to the next available number on entry into the trial, and each patient collected the pills directly from the pharmacy department at each center. The randomization code was developed using a computer random number generator to select random permuted blocks of 4, stratified by center. Only 1 pharmacist (P.G.) stored the randomization list and dispensed medication to each center according to it. All other members of the study group, as well as patients, were blind to group assignment.

Following baseline assessment, treatment with escitalopram or placebo was started 2 weeks before antiviral treatment. Escitalopram was used at a fixed dose of 15 mg/d (starting with 5 mg/d for the first week and 10 mg/d for the second). All patients received pegylated interferon alfa-2a (Pegasys, Roche Pharma, Basel, Switzerland) plus ribavirin (Copegus, Roche Pharma, Basel, Switzerland). Decisions about dosage and duration of antiviral treatment were made by treating gastroenterologists and were not controlled by study protocol.

Patients continued taking study medication for 14 weeks unless they dropped out or were terminated. The development of a major depressive episode at any point of the study

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resulted in study termination, without breaking the blind, and it was followed by standard psychiatric care. Duration of the study was decided to cover the period of greatest risk for new-onset depression[3,4,29] while limiting the burden of a prolonged treatment trial.

Patients were evaluated prior to administration of study drug, after 2 weeks (before starting pegylated interferon alfa-2a and ribavirin, considered the baseline point), and at weeks 4, 8, and 12 of antiviral treatment. In all cases, patients were assessed by both a gastroenterologist and a psychiatrist. Follow-up visits to assess viral response after study termination were done at weeks 24, 48, and 72.

Outcomes

The primary outcome to assess efficacy was the development of a major depressive episode at any time during the first 12 weeks of antiviral treatment, according to *DSM-IV*[26] criteria (except for duration—while *DSM-IV* criteria for a major depressive episode must be present during the same 2-week period, we specified that symptoms be present only within the same 1-week period). Diagnoses were made by a trained psychiatrist who applied the mood disorders module from the SCID-I/NP at each study evaluation. Other efficacy outcomes were the rate of antiviral dropouts and the evaluation of depressive symptom severity by applying the MADRS[30] and the Hospital Anxiety and Depression Scale (HADS).[31]

The MADRS is a 10-item, clinician-administered scale that is sensitive to symptom change during antidepressant treatment. It has been frequently used to measure depressive symptoms during interferon alfa therapy, and it exhibits improved internal consistency in patients with comorbid medical conditions compared with other clinician-administered questionnaires.[32]

The HADS is 14-item, patient-administered scale that allows 2 independent scores of depression and anxiety. It has been especially designed to apply to patients with comorbid medical conditions, as it excludes somatic or vegetative symptoms from the depression subscale.

We hypothesized that pretreatment with escitalopram would reduce the incidence of major depression and depressive symptoms during the first 12 weeks of antiviral treatment in CHC patients.

The primary outcome to assess safety was viral response, defined as the negativization of HCV RNA at different times. For patients with HCV genotypes 1 and 4, serum determinations were made at week 12 (interim assessment), week 48 (end of antiviral treatment), and week 72 (sustained virological response). Patients with HCV genotypes 2 and 3 were assessed at week 24 (end of antiviral treatment), and week 48 (sustained virological response). Other variables used for assessing safety were determinations of ALT at the same time points, as well as spontaneously reported adverse events and dropouts.

We hypothesized that pretreatment with escitalopram would be safe regarding adverse events and viral response in CHC patients during antiviral treatment.

Table 1. Characteristics of the Sample Before Allocation to Study Medication

Characteristic	Escitalopram (n = 66)	Placebo (n = 63)
Sex, n (%)		
Male	39 (59.1)	40 (63.5)
Female	27 (40.9)	23 (36.5)
Age, mean ± SD, y	46.7 ± 10.6	44.8 ± 10.8
HCV genotype, n (%)		
1	44 (66.7)	52 (82.5)
2	5 (7.6)	1 (1.6)
3	12 (18.2)	8 (12.7)
4	5 (7.6)	2 (3.2)
Serum analysis, mean ± SD		
ALT, U/L	110.7 ± 116.9	86.4 ± 60.9
Hemoglobin, g/dL	15.1 ± 1.3	15.1 ± 1.2
Neutrophil count, × 10^3/μL	3.4 ± 1.2	3.3 ± 1.1
Platelet count, × 10^3/μL	209.5 ± 53.1	208.1 ± 68.8
Past psychiatric history, n (%)		
Major depression	9 (13.6)	8 (12.7)
Alcohol use disorder	5 (7.6)	6 (9.5)
Opioid use disorder	5 (7.6)	8 (12.7)
MADRS score, mean ± SD	2.6 ± 3.5	2.3 ± 2.8
HADS-depression score, mean ± SD	2.5 ± 2.8	2.4 ± 2.5

Abbreviations: ALT = alanine aminotransferase, HADS = Hospital Anxiety and Depression Scale, HCV = hepatitis C virus, MADRS = Montgomery-Asberg Depression Rating Scale.

Statistical Analysis

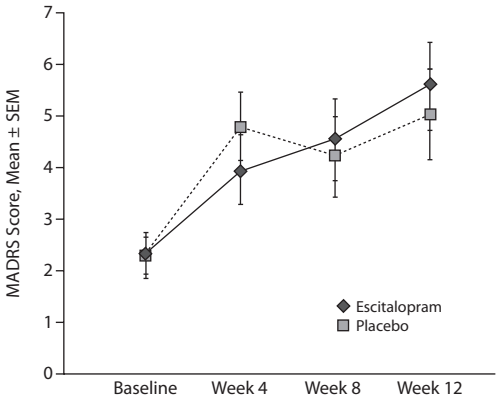
An intention-to-treat analysis was used. All patients who had received at least 1 dose of escitalopram or placebo were included in the analysis. Yates corrected χ^2 (or Fisher exact test when appropriate) was used to compare categorical variables, such as major depression and viral response. Continuous measures, such as MADRS or HADS scores at different points in time, were analyzed by 2-sided repeated measures analysis of variance. Factors included in the analysis were treatment group and visit number and the interaction between them. To solve the problem of missing data for patients who withdrew before completing the study because of the development of major depression, a procedure of last observation carried forward (LOCF) was used. For patients withdrawn for other reasons, however, this method would not be accurate. (We would be carrying forward scores of "nondepression.") So analyses have been done both including and excluding these patients. We present only data of LOCF excluding these patients, as results were similar including them. Two-sided significance tests were used throughout, and *P* values of less than .05 were considered to indicate statistical significance. Data were analyzed using SPSS statistical software version 15.0.1 (SPSS, Inc, Chicago, Illinois).

RESULTS

Characteristics of the Sample

One of 67 patients allocated to the escitalopram group and 3 of 66 in placebo did not receive the first dose of study medications (3 of them because of subject refusal and 1 because of changes in medical status). Consequently, 66 patients treated with escitalopram and 63 with placebo were included in the intention to treat analysis (Figure 1). Baseline characteristics of patients are shown in Table 1. All of the patients were

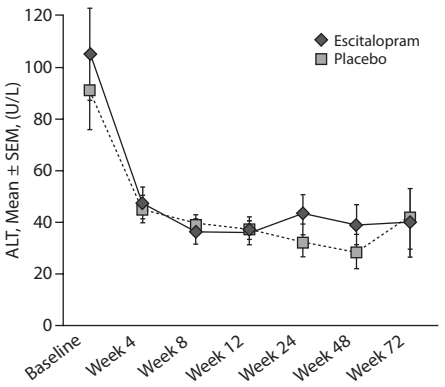
Figure 2. Mean (± SEM) MADRS Scores During the First 12 Weeks of Therapy With Pegylated Interferon Alfa-2a and Ribavirin in CHC Patients Randomized to Treatment With Either Escitalopram (n = 66) or Placebo (n = 63)[a,b,c]



Escitalopram	n = 66	63	60	59
Placebo	n = 63	59	58	54

[a]LOCF excluding patients withdrawn for reasons other than depression.
[b]The number of subjects in each group continuing in the study at each time point is indicated below the x-axis.
[c]Analysis of data showed that there was a significant effect of time on MADRS scores ($F = 14.103$, $P < .001$), but not of the interaction between visit and treatment group ($F = 0.900$, $P = .443$).
Abbreviations: CHC = chronic hepatitis C, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 3. Mean (± SEM) ALT (U/L) Along Antiviral Treatment With Pegylated Interferon Alfa-2a and Ribavirin in Genotype 1 CHC Patients Randomized to Treatment With Either Escitalopram (n = 66) or Placebo (n = 63)[a]



[a]There was a significant effect of time on ALT levels ($F = 11.052$, $P < .001$), but not of the interaction between visit and treatment group ($F = 1.124$, $P = .358$).
Abbreviations: ALT = alanine aminotransferase, CHC = chronic hepatitis C.

white. No statistically significant differences were found between groups.

All patients initiated pegylated interferon alfa-2a treatment with a dose of 180 μg, subcutaneously, weekly. Mean (SD) starting doses of ribavirin were 1,026.6 (142.8) mg/d for the placebo group and 1,009.1 (166.2) mg/d for the escitalopram group, with a range of 800–1,200 mg/d for both groups.

Efficacy

Seven of 129 patients (5.4%) met diagnostic criteria for *DSM-IV* major depression at any time during the first 12 weeks of antiviral treatment. No differences were observed in the development of major depression between those randomized to escitalopram vs placebo (5/66 [7.6%] with escitalopram vs 2/63 [3.2%] with placebo, Fisher exact test $P = .441$, odds ratio [OR] = 0.400; 95% CI, 0.075–2.141).

Four of 129 patients (3.1%) withdrew pegylated interferon alfa-2a and ribavirin treatment before week 12 for any reason, 1 of 66 (1.5%) in the escitalopram group and 3 of 63 (4.8%) in the placebo group. Differences were not statistically significant (Fisher exact test $P = .358$, OR = 3.250; 95% CI, 0.329–32.100).

Figure 2 shows MADRS scores by treatment group and across time. Analysis of data showed that there was a significant effect of time on MADRS scores ($F = 14.103$, $P < .001$), but not of the interaction between visit and treatment group ($F = 0.900$, $P = .443$). MADRS scores increased significantly during pegylated interferon alfa-2a and ribavirin treatment in both escitalopram and placebo groups. Post hoc analyses revealed that MADRS scores at all time points during treatment were significantly greater than MADRS scores at baseline in both groups ($P < .001$, after Bonferroni adjustment).

Figures for HADS-depression were similar (data not shown). Analysis of data showed that there was a significant effect of time on HADS-depression scores ($F = 3.139$, $P = .028$), but not of the interaction between visit and treatment group ($F = 0.149$, $P = .930$). HADS-depression scores increased significantly during pegylated interferon alfa-2a and ribavirin treatment in both escitalopram and placebo groups. Post hoc analyses revealed that HADS-depression scores were significantly greater at weeks 8 and 12 than at baseline and also at week 12 than at week 4 ($P < .05$, after Bonferroni adjustment).

Safety

Seventy-four of 107 patients (69.2%) with available data achieved sustained virological response, 36 of 53 (67.9%) in the escitalopram group and 38 of 54 (70.4%) in the placebo group. Fifty of 77 patients (64.9%) infected by genotype 1 achieved sustained virological response, 18 of 32 (56.3%) in the escitalopram group and 32 of 47 (71.1%) in the placebo group. No statistically significant differences were found between treatment groups, even though there was a trend for a lower antiviral response in the escitalopram group in genotype 1 patients (OR = 1.915; 95% CI, 0.740–4.953).

Figure 3 shows ALT analyzed at different points during treatment and follow-up and separated by treatment groups. Data are limited to genotype 1 patients. There was a significant effect of time on ALT levels ($F = 11.052$, $P < .001$), but not of the interaction between visit and treatment group ($F = 1.124$, $P = .358$). ALT levels decreased significantly during pegylated interferon alfa-2a and ribavirin treatment in both escitalopram and placebo groups.

Twelve subjects (6 [9.5%] treated with placebo and 6 [9.1%] with escitalopram) dropped out prior to study termination for reasons other than depression. Differences were

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Table 2. Prevalence of Treatment-Emergent Adverse Events Occurring in ≥ 10% of Patients During the First 12 Weeks of Therapy With Pegylated Interferon Alfa-2a and Ribavirin in CHC Patients Randomized to Treatment With Either Escitalopram or Placebo

Adverse Event	Escitalopram (n = 66), n (%)	Placebo (n = 63), n (%)	Odds Ratio	95% CI
Muscle or joint pain	22 (33.3)	32 (50.8)	2.065*	1.014–4.204
Fatigue	32 (48.5)	32 (50.8)	1.097	0.550–2.188
Skin problems	30 (45.5)	22 (34.9)	0.644	0.317–1.309
Respiratory symptoms	16 (24.2)	25 (39.7)	2.056	0.965–4.379
Sleep disturbance	23 (34.8)	23 (36.5)	1.075	0.523–2.210
Headache	18 (27.3)	19 (30.2)	1.152	0.537–2.471
Irritability	10 (15.2)	14 (22.2)	1.600	0.652–3.926
Nausea or vomiting	23 (34.8)	21 (33.3)	0.935	0.451–1.937
Flu-like symptoms	9 (13.6)	12 (19.0)	1.490	0.580–3.827
Dry mouth	14 (21.2)	17 (27.0)	1.373	0.610–3.089
Anxiety	10 (15.2)	11 (17.5)	1.185	0.465–3.020
Diarrhea	13 (19.7)	10 (15.9)	0.769	0.310–1.907
Hair loss	9 (13.6)	6 (9.5)	0.667	0.223–1.995
Fever	7 (10.6)	6 (9.5)	0.887	0.281–2.801
Loss of appetite	14 (21.2)	10 (15.9)	0.701	0.286–1.719
Sexual dysfunction	9 (13.6)	3 (4.8)	0.317	0.082–1.229
Dizziness	9 (13.6)	3 (4.8)	0.317	0.082–1.229
Leucopenia/neutropenia	7 (10.6)	4 (6.3)	0.571	0.159–2.056
Anemia	5 (7.6)	8 (12.7)	1.775	0.548–5.748

*$P < .05$.
Abbreviation: CHC = chronic hepatitis C.

not statistically significant ($\chi^2 = 0.007$, $P = 1.000$, OR = 1.053; 95% CI, 0.321–3.454). Six of them (4 [6.3%] with placebo, and 2 [3.0%] with escitalopram; Fisher exact test $P = .433$, OR = 2.169; 95% CI, 0.383–12.285) withdrew study medication because of intolerable side effects; and 6 (2 [3.2%] with placebo, and 4 [6.1%] with escitalopram; Fisher exact test $P = .681$, OR = 0.508; 95% CI, 0.090–2.877) were lost to follow-up. No patients were removed from the study as a result of active substance abuse.

No serious adverse event was reported. Other adverse events occurring in ≥ 10% of patients in at least 1 of the 2 groups of treatment are listed in Table 2. Muscle and joint pain was the only adverse event to be significantly less frequent in escitalopram-treated patients. No patient in either treatment group spontaneously expressed suicidal ideation nor did any patient develop symptoms consistent with mania or psychosis.

Finally, concomitant medications were used in a similar way in both treatment groups. Paracetamol (acetaminophen) was the only treatment that was significantly less used in the escitalopram group (18 [27.3%]) than in the placebo group (29 [46.0%]) (OR = 2.275; 95% CI, 1.092–4.739). The use of benzodiazepines (15 [22.7%] with escitalopram vs 19 [30.2%] with placebo, OR = 1.468; 95% CI, 0.668–3.228) and zolpidem (10 [15.2%] with escitalopram vs 10 [15.9%] with placebo, OR = 1.057; 95% CI, 0.407–2.742) did not show any significant difference between treatment groups.

DISCUSSION

Efficacy

This randomized, double-blind, placebo-controlled trial addressed the role of the antidepressant escitalopram in preventing pegylated interferon alfa-2a– and ribavirin–induced depression in CHC patients. A much smaller than anticipated percentage of patients met *DSM-IV* criteria for major depression during pegylated interferon alfa-2a and ribavirin treatment (5.4%). This low depression rate is even lower than in other recent studies in which new-onset major depression rates ranged from 11% to 16%,[24,33–35] but only slightly lower than in the other previous study by our group,[4] which found a rate of 8% of de novo major depression. This finding is in agreement with several studies relating interferon-induced depression with higher severity of depressive symptoms at baseline.[1,3,4,24,36–40]

No differences in the rates of major depression during the first 12 weeks of antiviral treatment were found between placebo and escitalopram groups. Moreover, no differences were found when MADRS and HADS-depression scores were evaluated as 2 different continuous measures of depression severity. These findings are not in agreement with the positive results shown in the first randomized controlled trial with prophylactic paroxetine in melanoma patients,[15] and they seem to disagree with several open trials with different SSRI antidepressants in CHC.[16–19] However, our results are in agreement with those found in 2 recent controlled studies in smaller samples of CHC patients,[23,24] even though Raison et al[24] actually found differences favoring the use of prophylactic paroxetine, but only after the first 12 weeks of antiviral treatment and in the group of patients with at least moderate scores on MADRS at baseline. Patients in our study completed only 12 weeks of antiviral treatment and had substantially lower MADRS depression scores at baseline (no patient exceeded scores for at least mild depression). For that reason, separate analyses for patients with depressive symptoms at baseline were not conducted. Moreover, differences in previous open trials in CHC[17–19] were found especially in psychiatric risk patients: Schaefer et al[18] in patients with mild-to-moderate depressive symptoms at baseline and/or a past history of psychiatric disorders; Kraus et al[17] in patients who had previously developed depression on interferon alfa therapy; and Gleason et al in patients with past history of depression.[19]

Taken together, these data confirm that CHC patients with no baseline psychiatric distress are unlikely to benefit from antidepressant prophylaxis, probably in contrast to other groups of psychiatric risk patients (with at least moderate scores on depression severity measures at baseline).[14,17–19,23,24]

Unrelated to depression, another finding that should be highlighted is that escitalopram worked significantly better than placebo in reducing rates of muscle or joint pain side effects and consequently also the rates of consumption of paracetamol (acetaminophen). This is related to the analgesic effects observed for paroxetine in patients receiving high-dose interferon alfa for cancer[15] and also in CHC patients.[24]

Safety

Regarding the safety of escitalopram in the outcome of antiviral treatment, we found that escitalopram used for 12 weeks at the beginning of pegylated interferon alfa-2a and

ribavirin treatment did not significantly affect either biochemical response or the negativization of HCV RNA and rates of sustained virological response, according to studies that found even better sustained virological response rates in patients who used antidepressants.[20,23] However, there was a trend in our study (although the differences were not statistically significant and probably not clinically significant) toward lower rates of HCV RNA negativization in genotype 1 CHC patients that deserves further study.

Regarding adverse events, treatment with escitalopram in our sample did not enhance the side effect burden of pegylated interferon alfa-2a and ribavirin. Moreover, side effects shared by antiviral therapy and SSRIs (diarrhea, headache, sleep disturbance) were not increased as a result of their combination. Finally, there was no evidence of increased suicidal ideation as a result of escitalopram administration.

Limitations

Several limitations of the current study warrant consideration. The low depression rate found may have underpowered our study to evaluate this outcome, even though there are no trends suggesting different conclusions. Patients in our study were biased by exclusion criteria that selected a group of much less depressive subjects than in other samples in the literature.[14,24] So, results may not be generalized to HCV populations with higher rates of current mood disturbance or with a greater burden of past psychiatric illness.[41,42] Neither can results be generalized to nonwhite populations or to HIV-coinfected patients. Moreover, monitoring of symptoms of depression and contact with mental health staff may have contributed to a lower rate of depression.

Our study was conducted over the first 12 weeks of antiviral treatment, the period of greatest risk for new-onset depression, as some[3,4,29]—but not all[22,24]—authors agree. Consequently, depressive episodes emerging later during treatment were not detected, therefore underestimating its incidence.[24]

The concomitant use of benzodiazepines could have also distorted results. However, benzodiazepines were used in a controlled way, at low doses, and with the same frequency between treatment groups.

Nor can we discount the influence of HCV genotype, even though in a previous study in which HCV genotype was evaluated as a risk factor for depression, no association was observed.[3] Our group[4] has previously found some differences among genotypes in the incidence of depression at baseline but not in interferon-induced depression.

In addition, the interferon formulation used in this study (pegylated interferon alfa-2a) could be associated with a lower incidence of psychiatric side effects compared to other interferon formulations. However, figures of depression associated with pegylated interferons seem to be quite similar to those of conventional formulations.[43,44] Moreover, there are no clinically significant differences between pegylated interferon alfa-2a and pegylated interferon alfa-2b regarding psychiatric side effects.[45]

Finally, the use of *DSM-IV* criteria for major depression or standard depression questionnaires probably do not identify accurately all psychopathological distress and symptoms induced by interferon and the potential benefits of antidepressants on irritability, pain or asthenia.

CONCLUSIONS

The findings do not provide support for antidepressant prophylaxis to prevent interferon-induced depression in CHC patients with low psychiatric risk. Further controlled studies directed to subpopulations of patients at high psychiatric risk are clearly warranted. On the other hand, the use of escitalopram in CHC patients is well tolerated, and safe regarding biochemical and viral response.

Drug names: escitalopram (Lexapro and others), paroxetine (Paxil, Pexeva, and others), ribavirin (Rebetol, Copegus, and others), zolpidem (Ambien, Zolpimist, and others).

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