

PREDICTIVE FACTORS OF SEVERE TOXICITY ASSOCIATED WITH PEGYLATED INTERFERON AND RIBAVIRIN TREATMENT IN HIV/HCV-COINFECTED PATIENTS

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GRUPO PARA EL ESTUDIO DE LAS HEPATITIS VIRICAS DE LA SOCIEDAD ANDALUZA DE ENFERMEDADES INFECCIOSAS

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ABSTRACT

BACKGROUND: Dose reductions or premature discontinuation of treatment due to severe adverse effects related to pegylated interferon (PEG-IFN) and ribavirin (RBV) is relatively common among HIV/HCV-coinfected patients. However, the possible risk factors of severe toxicity associated with PEG-IFN and RBV treatment are unknown.

OBJECTIVE: The aim of our study was to identify predictive factors associated with severe toxicity secondary to the combination of PEG-IFN plus RBV in HIV-infected patients with chronic hepatitis C.

PATIENTS AND METHODS: All HIV/HCV-coinfected patients who received at least one dose of PEG-IFN alpha-2a (180 µg weekly) or PEG-IFN alpha-2b (1.5 µg/K weekly) plus RBV (800-1200 mg/day) from October 2001 to February 2005 at nine hospitals in Spain, were included in the study. Severe toxicity associated with PEG-IFN and RBV combination was defined as an episode of laboratory abnormality (hemoglobin level <10 g/dL, neutrophil counts < 750/mm³, platelet counts <50000/mm³ or TSH > 10 mIU/mL) or clinical side effect which led to permanent discontinuation of treatment. Univariate and multiple logistic regression analysis were performed to determine baseline variables associated with severe toxicity, included pre-treatment hematological levels, use of specific antiretroviral drugs and those related with anti-HCV therapy.

RESULTS: Two hundred and thirty-seven HIV/HCV-coinfected patients were included in this study. A total of 198 (34%) subjects received concomitant antiretroviral therapy. Sustained virologic response and premature discontinuation of therapy due to adverse events were observed in 87 (37%) and 30 (13%) individuals, respectively. Ninety-four (40%) patients developed some event of severe toxicity. Neutropenia (18%) and influenza-like syndrome (4%) were the most frequent severe laboratory abnormality and clinical adverse event, respectively. In the multivariate analysis, zidovudine treatment (adjusted odds ratio [AOR] 2.9, 95% CI 1.4-5.9; p=0.002), didanosine treatment (AOR 3.7, 95% CI 1.2-10.9; p=0.015), cirrhosis (AOR 3.0, 95% CI 1.2-7.1; p=0.01), history of depression (AOR 3.4, 95% CI 1.2-9.5; p=0.014) and hemoglobin level < 14 g/dL (AOR 5, 95% CI 2-10; p<0.001) were associated with severe toxicity.

CONCLUSIONS: Antiretroviral regimens including zidovudine or didanosine, liver cirrhosis, baseline hemoglobin level lower than 14 g/dL and a history of depression are predictors of severe toxicity secondary to PEG-IFN plus RBV among HIV/HCV-coinfected patients.

BACKGROUND

A worse tolerability of pegylated interferon (PEG-IFN) plus ribavirin (RBV) combination could partially explain a lower efficacy to this therapy in subjects coinfected with HIV and hepatitis C virus, particularly in those receiving antiretroviral therapy, compared with those with HCV infection alone. Thus, side effects related with PEG-IFN-based therapy may be treatment limiting and require temporary or permanent dose reductions or premature discontinuation. This may negatively affect the probability of achieving sustained virologic response in this population.

Therefore, there is a need for further research aimed to improve the management of these adverse events, particularly concerning the identification of factors that contribute to the development of some type of significant toxicity. However, to date, the possible risk factors of severe toxicity associated with PEG-IFN and RBV treatment in HIV/HCV-coinfected patients are unclear.

OBJECTIVE

To identify predictive factors associated with severe toxicity secondary to the combination of PEG-IFN plus RBV in HIV-infected patients with chronic hepatitis C.

PATIENTS AND METHODS

Patients

HIV/HCV-coinfected patients (age ≥ 16 years) with quantifiable serum HCV-RNA level followed in nine hospitals in southern Spain.

Study design

All individuals who received at least one dose of PEG-IFN alpha-2a (180 µg weekly) or PEG-IFN alpha-2b (1.5 µg/K weekly) plus RBV (800-1200 mg/day) from October 2001 to February 2005 were included in a retrospective study. Patients fulfilled the following pretreatment hematological criteria: i) hemoglobin level higher than 11 g/dL ii) neutrophil counts higher than 1000 cells/mm³; iii) platelet counts higher than 70000 cells/mm³.

Treatment duration was 24 weeks for subjects harboring HCV genotype 1 or 4, and 48 or 48 weeks for patients with HCV genotypes 2 or 3. At weeks 12 and 24, HCV therapy was prematurely discontinued in those non-responders individuals. Temporary discontinuations and stepwise reductions in PEG-IFN and RBV dosage, and the use of granulocyte colony-stimulating factors and erythropoietin were done according to the decision of the caring physician.

Assessment of severe toxicity

The main outcome variable was severe toxicity associated with PEG-IFN and RBV combination, defined as an episode of laboratory abnormality (hemoglobin level <10 g/dL, neutrophil counts < 750/mm³, platelet counts <50000/mm³ or TSH > 10 mIU/mL) or a clinical side effect which led to permanent discontinuation of treatment.

Statistical analysis

Univariate and multiple logistic regression analysis were performed to identify factors predictive of severe toxicity. Likewise, predictors of each type of hematological adverse event were also assessed in different subanalysis. The following variables were included: age, sex, presumed route of transmission, body-mass index, body weight, baseline CD4+ cell count, undetectable HIV-RNA at baseline, diagnosis of AIDS, use of individual antiretroviral drugs, HCV genotype, baseline ALT level, liver fibrosis stage, type of PEG-IFN given, daily dose of RBV by weight and pretreatment hematological parameters.

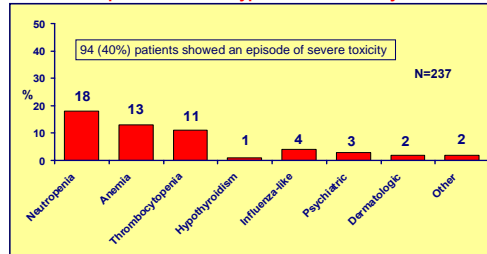
RESULTS

Features of the study population

Characteristics	Patients n= 237
Age (years)*	39 (35-42)
Male sex, no (%)	202 (85)
Body-mass index (K/m ²)*	23 (21-25)
AIDS, no (%)	69 (29)
Baseline log HCV viremia (IU/mL)*	5.9 (5.5-6.2)
Baseline ALT level (IU/mL)*	91 (58-136)
HCV genotype 1-4, no (%)	147 (62)
PEG-IFN alpha-2a, no (%)	184 (78)
Advanced liver fibrosis (F3-F4), no (%)†	86 (52)
RBV dose/weight (mg/K/day)*	13.9 (12.4-15)
History of depression, no (%)	26 (11)
Baseline CD4+ cell count (cells/mm ³)*	532 (379-723)
Baseline undetectable HIV-RNA viral load, no (%)	165 (70)
Concomitant antiretroviral therapy, no (%)	198 (83)
Use of zidovudine (AZT), no (%)‡	62 (31)
Use of didanosine (ddl), no (%)‡	18 (9)
Use of stavudine (d4T), no (%)‡	66 (33)
Protease inhibitor (PI)-based therapy, no (%)‡	86 (43)
NNRTI-based therapy, no (%)‡	96 (49)
Baseline hemoglobin level (g/dL)	15 (13.9-16)
Baseline neutrophil counts (cells/mm ³)*	2780 (2157-3785)
Baseline platelet counts (cells/mm ³)*	174000 (128000-307000)
Sustained virologic response, no (%)	87 (37)

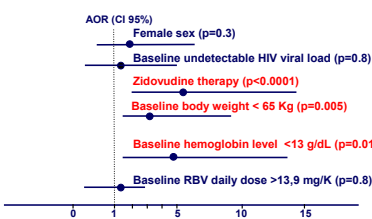
*median (interquartile range). †Liver biopsy available in 165 patients. ‡The percentages showed were calculated in the population who received ART.

Frequencies of each type of severe toxicity

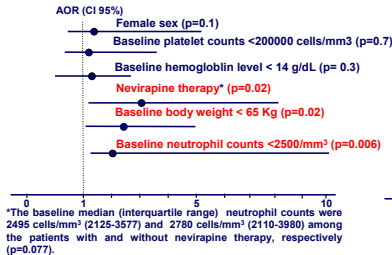


30 (13%) patients discontinued HCV therapy due to severe side effects. Only 4 (2%) individuals were prematurely withdrawn from PEG-IFN plus RBV because of haematological side effects. Among the 80 (34%) individuals developing severe haematological toxicity, dose reductions of PEG-IFN or RBV occurred in 56 (70%) subjects.

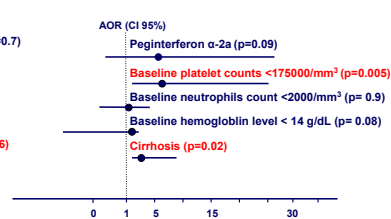
Factors associated with severe anemia



Factors associated with severe neutropenia



Factors associated with severe thrombocytopenia



CONCLUSIONS

- Antiretroviral regimens including zidovudine or didanosine, liver cirrhosis, baseline hemoglobin level lower than 14 g/dL and a history of depression are predictors of severe toxicity secondary to PEG-IFN plus RBV among HIV/HCV-coinfected patients.
- Low pretreatment levels of each hematological line predict severe decrease of their values during HCV therapy.
- Patients with low baseline body weight are more likely to develop significant anemia and neutropenia.