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Prospective, observational real-life study on eligibility for and outcomes of antiviral treatment with peginterferon α plus ribavirin in chronic hepatitis C☆

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ABSTRACT

Background: We aimed to investigate eligibility, reasons for treatment discontinuation and characteristics of chronic hepatitis C patients with treatment failure to peginterferon/ribavirin in clinical practice.
Methods: 1128 chronic hepatitis C patients, from 45 Italian Hepatology centres, were enrolled in this phase-4, prospective, observational study from January 2009 to February 2010.
Results: 687/1118 patients (61.4%) were eligible for antiviral treatment, of which 598 (87.0%) agreed with the physician's decision. Outcome information was available in 500/598 patients, among whom 348 (69.6%) completed treatment. Treatment was discontinued in 152 patients due to: lack of response (28.9%), personal reasons (29.6%), adverse events (38.2%), and decompensation (1.3%). Sustained virological response was obtained in 263/500 (52.6%), 71 (14.2%) relapsed and 61 (12.2%) were non-responders. Treatment outcome was not available in 105 (21%): lost while receiving treatment (33.3%), lost during follow-up (25.7%), withdrawn for adverse events (19.1%) or for administrative reasons (21.9%).
Conclusion: In clinical practice, only 61% of chronic hepatitis C patients are considered eligible for peginterferon/ribavirin. Of these, 13% refuse treatment. Approximately 30% do not complete the scheduled treatment and, despite this, the sustained virological response rate is similar to that of randomized-controlled trials. In the era of new antiviral combinations, these findings have important implications for assessing eligibility and estimating drop-out rates.

1. Introduction

Chronic hepatitis C (CHC) represents an important public health problem in Italy with an estimated 1.5–2 million chronic carriers [1]. Italy has the highest prevalence rates of hepatitis C virus (HCV) infection in Europe (3–4.4%), with the highest rates of 12.6–26% in the Southern regions and major islands [2]. Chronic HCV infection is an important cause of morbidity and mortality in Italy. It is the leading cause of mortality from liver cirrhosis and hepatocellular carcinoma (HCC) and is the leading indication for liver transplantation [3].

In Italy, CHC is treated in approximately 600 centres. However, nationwide data concerning HCV disease management in real practice, particularly the reasons for treatment failure, are limited.

In the next 10 years, approximately 400,000 people are expected to be at risk of developing complications from liver disease [4]. Antiviral therapy is burdened by a significant percentage of dropouts, often due to poor treatment tolerance and suboptimal management of adverse events (AEs). Over the past decade, the current standard-of-care for treatment of CHC has been the combination of pegylated interferon α plus ribavirin (Peg-IFN/RBV). In Italy, the approval of the two protease inhibitors (boceprevir and telaprevir) has made a new standard-of-care available for patients infected with the HCV genotype (G) 1 [5]. HCV antiviral therapy research is advancing rapidly; therefore, many other IFN-sparing regimens are now in development for the treatment of CHC. Recently, the Italian Regions have issued guidelines for triple treatment of patients with hepatitis C that limit such treatment to a small number of centres, specify strict eligibility criteria and require more intense clinical monitoring of patients being treated. This monitoring will require a major reorganization of

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the service network. A better understanding of the burdens of the actual clinical routines is essential to streamline diagnostic and therapeutic strategies, to overcome existing barriers of access and to ensure more appropriate management of antiviral treatments. Furthermore, we believe that describing what happens in practice will provide the information needed for the appropriate and efficient use of resources in the era of new antiviral drugs.

1.1. Study hypotheses and objectives

This project was designed to collect prospectively, through the development of a specific database, the data needed to identify the characteristics of eligibility to and of the management and outcomes of antiviral therapy in real clinical practice in Italy.

The primary objective of this study was to determine the reasons for ineligibility to antiviral treatment.

The secondary objective of the study was to evaluate the virological outcomes and the characteristics of patients showing treatment failure with dual antiviral therapy.

2. Methods

2.1. Study design

This was a non-interventional, prospective, observational, phase 4, multicentre study.

Consecutive patients of both sexes presenting with CHC and a documented genotype at any of the 45 participating centres from January 2009 to February 2010 (enrolment frame time) were included in the study if they satisfied the inclusion/exclusion criteria. During the study period, the standard first-line therapy was offered to CHC patients in all participating centres.

All study activities were consistent with Circular n. 6, September 2nd, 2002 and with the definition of non-interventional studies reported in EU Directive 2001/20/EC. The study drug was prescribed in the usual manner according to the terms of the marketing authorization. The assignment of a patient to a particular therapeutic strategy was not decided in advance by the trial protocol but was based on current practice, and the prescription of treatment was independent of the decision to include the patient in the study. No additional interventions that are not used in general practice, such as extra blood sampling, were applied to the enrolled patients.

Two visits were planned. During the baseline visit, informed consent was obtained, the inclusion/exclusion criteria were reviewed, and the medical history was obtained. If the decision was made to treat the patient, a second visit was planned at 24–48 weeks after the initiation of treatment. Finally, outcome evaluation was performed 24 months after the end of treatment.

Patients were consecutively enrolled in the study. The study was sponsored by Merck (formerly Schering-Plough S.p.A.) and was registered as ClinicalTrials.gov Identifier: NCT00724451.

2.2. Selection of study population

The inclusion criteria were documentation of written informed consent, either gender $\geq$18 years of age, diagnosis of CHC, serum positive for HCV-RNA, and no history of previous treatment with Peg-IFN. The exclusion criteria were previous treatment with Peg-IFN, participation in a therapeutic good clinical practice study within 30 days prior to the beginning of this study, unwillingness to participate, and age <18 years. The patient could be enrolled only after an informed consent was signed. The patient was considered to have completed the study upon completion of the last protocol-specified contact (e.g.: visit or telephone contact with the principal investigator or qualified designee).

2.3. Ethics

The study protocol was approved by the local Ethical Committees of all participating centres, and a signed consent form was obtained from each eligible patient upon recruitment. The study protocol conforms to the ethical guidelines of the "World Medical Association (WMA) Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Patients" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008.

2.4. Statistical analysis

Prior to locking the database, a detailed Data Analysis Plan was completed and filed. The Data Analysis Plan contains the rules and data-handling conventions used to perform the analyses and the procedures used to account for missing data.

2.5. Demographic and other baseline characteristics

Demographic (sex, race, age, weight, body mass index, etc.) and baseline clinical variables (HCV viral load, transaminases, laboratory data, HCV genotype, alcohol intake, presence of fibrosis/cirrhosis, presence and type of active comorbidities, etc.) were summarized for all patients regardless of whether they were treated with the antiviral therapy. Summary statistics (number of cases, mean, median, standard deviation, minimum, and maximum) were calculated for the continuous variables; the number and the percentage of patients in each category were calculated for the categorical variables. The demographic and clinical characteristics of treated and untreated patients were compared using the chi-square test for categorical variables and the *t*-test for quantitative variables. The analyses included all screened patients. Because data were not available for all patients initially included in the statistical analyses, efficacy analysis was performed using both an *intention-to-treat* and a *per-protocol* approach.

2.6. Qualitative data

In the Case Report Form, qualitative questions were frequently used to avoid the induction, on participating physicians, of standardized answers. A qualified "Data Interpretation Committee" coded the free text format answers at the end of the clinical phase.

2.7. Analysis of primary endpoint

The reasons for non-eligibility to antiviral therapy were analysed using descriptive methods (frequency and percentage).

2.8. Analysis of secondary endpoint

The reasons for withdrawal from the antiviral therapy were investigated using descriptive methods, and the efficacy data were reported as frequencies.

2.9. Safety analysis

The frequencies of withdrawal and discontinuation of the treatment/study due to AEs were tabulated. A formal analysis of AEs and laboratory data was not performed because the study was a phase 4 study sponsored by Merck (formerly Schering-Plough S.p.A.). Only the safety data concerning the Schering-Plough products were available. Therefore, a safety analysis was excluded from the study objectives.