1.0 Abstract

Title

Quality of life measurement using wrist actigraphy in HCV genotype 1 infected, treatment naïve patients suffering from fatigue and receiving ombitasvir, paritaprevir, and ritonavir tablets and dasabuvir tablets (Viekirax®/Exviera®; 3D regimen): The HEMATITE Study

Keywords

Hepatitis C, Mean Daytime Physical Activity, Fatigue, Quality of Life, Activity Tracker

Rationale and Background

Physical and mental fatigue is the most common symptom reported by patients with Hepatitis C Virus (HCV), which highly impacts their overall quality of life. AASLD (American Association for the Study of Liver Diseases) and EASL (European Association for the Study of the Liver) guidelines therefore rate the treatment of HCV patients suffering from fatigue as a high priority. This cardinal symptom presents regardless of the stage of liver fibrosis and is difficult to quantify objectively. Similar to other potential reasons for physical fatigue, such as hepatic encephalopathy, increasing evidence suggests a direct viral impact on the central nervous system (CNS). Data demonstrating a longitudinal change of physical fatigue and increased daytime physical activity upon treatment with 3D regimen are missing to date and are anticipated by the Swiss scientific HCV community [1, 2].

The rationale for this observational study is to observe the impact of therapy with 3D regimen on physical activity of HCV patients suffering from fatigue. Furthermore, this study supports the Swiss Hepatitis Strategy, which seeks for the elimination of viral hepatitis in Switzerland within the next 15 years by creating awareness for patients with extrahepatic manifestations [3].

Research Question and Objectives

Does successful treatment with 3D regimen increase total daytime physical activity and reduce fatigue in HCV-positive patients?

Primary objective:

- To observe changes in physical activity in patients with newly initiated therapy with 3D regimen between pre-treatment (baseline) and post-treatment week 12

Secondary objectives:

- To correlate subjective fatigue (assessed by means of Fatigue Severity Scale [FSS]) and physical activity (measured with an electronic activity tracker) at baseline, during and after 12 weeks of treatment with 3D regimen
- To observe the proportion of patients achieving sustained virologic response (SVR12) after treatment with 3D regimen (defined as HCV not detectable, 12 weeks after the last dose of 3D regimen)
- To observe sleep efficiency (assessed by means of activity tracker) at baseline, during and after 12 weeks of treatment with 3D regimen

Study Design

HEMATITE is an observational, prospective, open label, single-arm, multi-centric, real-life study in HCV-positive patients (genotype 1).

Setting

The study consists of a treatment preparation phase of 4 weeks to obtain baseline physical activity by use of a wrist-worn activity tracker, a treatment phase (12 weeks) and a follow-up phase (12 weeks) to evaluate treatment response. The activity tracker is worn for 4 weeks before each visit, to obtain stable individual activity data. At every visit, questionnaire-based fatigue is recorded (FSS questionnaire), according to routine clinical care.

Subjects and Study Size, Including Dropouts

Population:
Patients are eligible for observation in this study, if the following applies:

Inclusion Criteria:
- Male and female patients aged ≥ 18 years
- Treatment-naïve patients
- Patients mono-infected with CHCV, GT1 (confirmed within the last 36 months or at physician's discretion in case of risk factors)
- Non-cirrhotic patients (based on liver biopsy, fibroscan ≤ 9.6kPa and/or clinical signs)
- The decision to treat with 3D regimen is made by the physician in accordance with the local Swiss product label prior to any decision to approach the patient to participate in this study. [4]
- Patients with fatigue (FSS ≥ 4)
- Patients willing to participate in the study, and willing to wear an activity tracker

Exclusion Criteria:
- Patients with sources of fatigue other than HCV (especially, severe depression (Annex 4), cancer and hormonal disorders causing clinically significant fatigue)
- Patients with conditions that do not allow to adhere to protocol and use of the device at investigator's discretion
- Patients being wheelchair dependent

Study Size:
Approximately 100 patients in Switzerland will be enrolled.

Variables and Data Sources

Variables:

Primary Variable

- Change of mean daytime physical activity between baseline (before treatment start) and post-treatment week 12

Secondary Variables

- Change of Fatigue Severity Score (FSS) between baseline, during and after 12 weeks of treatment with 3D regimen
- Correlation between mean daytime physical activity and FSS at baseline, during and after 12 weeks of treatment with 3D regimen
- Proportion of patients achieving SVR12 after treatment with 3D regimen (defined as HCV RNA not detectable 12 weeks after the last actual dose of 3D regimen)
- Sleep efficiency at baseline, during and after 12 weeks of treatment with 3D regimen

Data Sources:

Source documents are defined as original documents. The investigator will document patient data, including FSS, in his/her own patient files which will serve as source data for the study. Physical activity and sleep data will be collected by use of wrist-worn activity trackers (ActiGraph GT9X Link) which will be processed by device-specific software (ActiLife 6) to obtain the activity and sleep-related variables for analysis (Annex 1). All data collected by the activity tracker will be analyzed by the biostatistician at the end of the study. The data will not be seen by the investigators and patients at any time during data collection (between visit 1 and visit 5 (Figure 1: Study Activities).

Results

Within the HEMATITE study 82.2 % (n = 37) of the enrolled patients (n = 45) had at least one more visit after the screening visit and also had tracker data available. The change of mean daytime physical activity, which was recorded by tracker was analyzed as primary outcome parameter by comparing mean daytime physical activity at baseline (V2) and post-treatment week 12 (V5). This analysis provided no statistically significant difference between the visits (p = 0.091, one-sample t-test). In contrast Fatigue Severity Scale (FSS), one of the secondary outcomes, degreased significantly during the study course (p < 0.001, paired Wilcoxon test). For FSS score a mean reduction of 2.8 (95% CI: 2.21, 3.43) from baseline (Day 1) to 12 weeks post-treatment (Day 168) was observed. Sleep efficiency, the second parameter recorded by tracker and also the second outcome parameter, showed no difference between baseline and post-treatment week 12 visit (p = 0,381, paired Wilcoxon test). All but one patient treated with 3D regimen achieved viral elimination as determined by undetectable HCV RNA 12 weeks post-treatment (SVR12) so the 93.7% of patients achieved SVR12 in the scale down ITT population. The planned subgroup analyses – Ribavirin, sex, fibrosis stage, age and chronic hepatitis C infection – almost delivered no differences between the groups for the primary and secondary outcome parameters. During the study 52.18% (n = 21) of 41 patients experienced an AE, 31.7% experienced an AE considered related to study drug, and no SAE was observed. None of the AEs were procedure-related or led to discontinuation.

Discussion

This observational study examined the impact of treatment with 3D regimen on HCV patients suffering from fatigue. For mean daytime physical activity, no was observed from baseline (V2) to post-treatment week 12 (V5). In contrast Fatigue Severity Scale degreased notably (2.8 score points, 95% CI: 2.21, 3.43) during the study course. The lack of correlation between these parameters may be partly explained by the fact that a high proportion of jobs are sedentary and most working conditions do not allow for large

changes in physical activity. Conceivably the differences in physical activity may be too small to be detected by the activity tracker and studies have shown that they may not accurately detect light physical activity such as washing dishes, cooking food and walking slowly [40].

Differentiating between HCV-associated and non-associated fatigue and physical inactivity is difficult [41]. In our study patient, fatigue was independent of gender, age, fibrosis stage and genotype 1 subtype. Furthermore 26.8 % of the patients have been reported to have overweight (BMI ≥ 25), 61.0 % consumed alcohol and 51.2 % were smokers at screening. These factors may have contributed to fatigue and a lack of physical activity in patients during the study. Also despite its hemolytic characteristics and thus potential to cause anemia [43] both mean daytime physical activity as well as FSS were not impacted by the co-administration of ribavirin [11].

All but one patient achieved viral elimination determined by undetectable HCV RNA 12 weeks post-treatment (SVR12) so 97.3% of patients achieved SVR12.

During the study, there were no SAEs related to study drug or AEs that led to discontinuation. The observed AE profile was in line with that previously reported [24, 47] therefore the 3D regimen was well-tolerated.

Marketing Authorization Holder(s)

AbbVie AG Schweiz

Names and Affiliations of Principal Investigators