Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment

Vladimir T Ivashkin1, Igor V Maev2, Chavdar S Pavlov1, Marina V Mayevskaya1, Aleksey A Samsonov2, Lyudmila K Palgova3 and Kirill M Starostin**

1I.M. Sechenov First Moscow State Medical University, Ministry of Health of Russia, Moscow, Russia
2A.I. Evtokimov Moscow State University of Medicine and Dentistry, Ministry of Health of Russia, Moscow, Russia
3Clinical Research and Educational center in Gastroenterology and Hepatology of St Petersburg Universitetskaya Naberezhnaya, Saint Petersburg, Russia
4CHC Medical, Sanofi, Moscow, Russia

*Corresponding Author: Kirill M Starostin, CHC Medical, Sanofi, Moscow, Russia.

Received: March 14, 2020; Published: April 10, 2020

Abstract

Background/Aims: Steatosis is a key contributor to non-alcoholic fatty liver disease (NAFLD) pathogenesis, serving as an essential step towards further disorders, including inflammation and non-alcoholic steatohepatitis (NASH). Essential phospholipids are used as adjuvant treatment in people with fatty liver disease and other chronic liver diseases. A new formulation of essential phospholipids paste (ESSENTIALE®, Sanofi) has been developed to make the daily dosing regimen more comfortable and simple and to improve patient compliance. The study was aimed to assess the safety, patient-reported outcomes and impact on compliance of the new essential phospholipids paste formulation in patients with NAFLD and viral hepatitis.

Methods: The study enrolled 147 patients (48.3% male; mean ± standard deviation [SD] age 44.8 ± 10.5 years) in the intention-to-treat population; 72.8% had NAFLD and 27.9% had viral hepatitis B or C. Patients received essential phospholipids paste (one 600 mg sachet 3 times daily) for 12 weeks, with 4-, 8-, and 12-week scheduled visits and a 13-week follow-up visit. Patient-reported outcomes were evaluated using Global Overall and Gastrointestinal Symptom scales and Likert 7-point score scale changes at 4, 8 and 12 weeks compared with baseline. Compliance was assessed by comparing actual versus prescribed dosing of essential phospholipids.

Results: After 12 weeks treatment with essential phospholipid paste, statistically significant improvements from baseline in mean ± SD Global Overall Symptom scores (from 4.21 ± 1.09 to 1.87 ± 0.91; P < 0.01) and overall Gastrointestinal Symptom scores (from 19.91 ± 5.74 to 11.17 ± 3.57; P < 0.01), were observed. Compliance with prescribed essential phospholipid treatment was 99% throughout the 12-week treatment period.

Conclusion: Essential phospholipids paste had a favorable safety profile associated with improved symptoms and with high levels of compliance over 12 weeks in patients with NAFLD and viral hepatitis accompanied by gastrointestinal symptoms.

Keywords: Non-Alcoholic Fatty Liver Disease; Symptoms; Gastrointestinal Dysfunction; Essential Phospholipids; Phosphatidylcholine; Liver Disease

Citation: Kirill M Starostin., et al. "Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment". EC Gastroenterology and Digestive System 7.5 (2020): 10-21.
Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of liver transplantation. The incidence of NAFLD in cryptogenic liver cirrhosis is up to 75% [1]. A diagnosis of NAFLD is associated with a 34% - 69% increase in the risk of death of over 15 years [2] and the prevalence of NAFLD is gradually increasing worldwide [3]. According to the DIREG2 study, the prevalence of NAFLD in Russia in 2015 was more than 37% and had increased by 10% compared with 2007 [4]. Fatty liver disease also raises concerns because of its latent evolution and association with other diseases, including type 2 diabetes (T2DM) and obesity [4]. NAFLD is known to be associated with a four-fold increase in the risk of cardiovascular disease and up to three-fold increase in the risk of cardiovascular death [5,6]. There is increasing evidence to suggest an association between NAFLD and a higher risk of gastrointestinal disorders, including cholelithiasis, gastroesophageal reflux disease (GERD), and hepatocellular carcinoma, as well as an increased risk of breast cancer in women and colorectal cancer in men [7-9]. Severe exacerbation of chronic pancreatitis has also been observed in patients with NAFLD [10].

The current therapy of NAFLD primarily includes lifestyle changes, weight loss, and treatment of comorbidities [11]. However, no gold standard pharmacotherapy for NAFLD currently exists. Several promising molecules are being investigated, and a number of pharmacotherapeutic options are applied in clinical practice [12]. Among the existing hepatoprotective interventions available, essential phospholipids (EPL) are the most studied pharmacologic therapy in NAFLD, especially with regard to their impact on steatosis [11,13]. The efficacy of EPL in reducing steatosis was shown in six randomized controlled trials, based on ultrasound, computer tomography (CT), and liver histology assessments [14-19]. Polyenyl phosphatidylcholine (PCH), a key component of EPL, has membranous, antioxidative, and antifibrotic effects and may be characterized as a pathogenetic-based treatment of NAFLD [13]. Furthermore, EPL has a favorable safety profile, with no serious adverse events (AEs) and transient non-serious AEs observed during its use [13,20]. NAFLD is not characterized with any highly specific symptoms, however a variety of non-specific systemic and gastrointestinal symptoms may accompany this condition impairing patients quality of life [21].

EPL may also be used as an adjuvant intervention in patients with viral hepatitis [20]. The highest prevalence rate of NAFLD has been reported in patients with hepatitis C (HCV) and hepatitis B (HBV): 55% and about 22%, respectively [22]. Viral hepatitis are usually associated with impaired quality of life and non-specific gastroenterology symptoms [23]. EPL can be used as part of complex appropriate treatment because of its contribution to histological improvement in viral hepatitis [20]. Based on evidence regarding the benefits of EPL in people with viral hepatitis [19,24-26] and the presence of virus-associated steatosis in patients with viral hepatitis, which is expected to exacerbate disease progression and worsen prognosis [22,27], EPL therapy in patients with fatty liver and viral hepatitis may also be valuable from a clinical point of view.

In most studies of patients with NAFLD, the therapeutic efficacy of EPL was demonstrated at a daily dose of 1800 mg [13]. When considering the active component, the amount of PCH contained in an effective therapeutic dosage of EPL is estimated at 1368 mg daily. In the Russian Federation, over-the-counter EPL is currently available in capsule formulation (Essentiale Forte® 300 mg, Sanofi), which requires the patient to take six capsules per day (two capsules three times daily) to achieve the recommended dose. Given the required frequent administration, the patient's adherence to EPL treatment may be reduced [28]. Furthermore, the capsule formulation may be difficult to swallow for certain patient populations, such as the elderly, children, or patients with dysphagia [29]. Generally, up to 40% of
adults experience difficulty in swallowing tablet or capsule formulations [30]. Therefore, changing the formulation of the medication may allow for more comfortable and easier administration in these patients [30].

The present study investigated the safety and patient-reported outcomes of a new dosage form of EPL, a PCH-containing paste, in Russian patients with NAFLD or viral hepatitis. The paste is available in sachets, each containing 600 mg of EPL. Due to the increased dose compared with capsule formulation, the EPL paste can be administered as one sachet three times daily. Although the number of daily doses remains unchanged, dosing is less complex, which is an important factor affecting treatment adherence and compliance with the dosing regimen [28]. In particular, taking one pill at a time instead of two increases adherence [31].

Materials and Methods

Study design and patient population

This multicenter, interventional, open-label, prospective, non-controlled phase III clinical study assessed the safety and clinical patient-reported outcomes (effectiveness) of 600 mg of EPL paste administered orally thrice daily (1800 mg daily of EPL) in patients with NAFLD or viral hepatitis accompanied by clinical gastrointestinal symptoms.

The study was conducted at eight sites in Russia: Department of Internal Medicine, Medical Faculty, I.M Sechenov First Moscow State Medical University, Ministry of Health of the Russian Federation, Moscow; Moscow State University of Medicine and Dentistry named after A.I. Evdokimova, Central Clinical Hospital № 2 named after N.A Semashko, Moscow; Nizhny Novgorod Regional Clinical Hospital named after N. A. Semashko, Federal Privolzhsky Gastroenterological Center, Nizhny Novgorod; Professor’s Clinic of Kazan State Medical University, Kazan (Site of Kazan State Medical University); Northern Medical Clinical Center named after N.A Semashko, Arkhangelsk; City Hospital № 26, Saint-Petersburg; City Emergency Hospital № 2, Rostov-on-Don; and LLC “PolyKlinika Expert”, Saint-Petersburg.

The study protocol complied with the recommendations of the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines for good clinical practice (GCP). The protocol also complied with all applicable Russian laws, regulations and guidelines. Ethical approval was granted by the Russian Healthcare Ministry Ethics Committee. All study participants provided written informed consent prior to study inclusion. Study details are disclosed at clinicaltrials.gov (NCT02517385).

The duration of the study was 14 weeks, with five planned visits (1 week of prescreening, 12 weeks of treatment, and 1 week of follow-up). Physicians and gastroenterologists at the in-patient departments of the study sites carried out the recruitment and all interventions. Eligible patients were aged 18 - 65 years and had gastrointestinal symptoms in the presence of NAFLD (a diagnosis of NAFLD confirmed on ultrasound) or viral hepatitis (based on appropriate clinical and laboratory assessments), without signs of severe fibrosis or liver failure. Only patients receiving standard therapy for the underlying liver disease were included in the study. The exclusion criteria were: age < 18 or > 65 years; pregnancy or lactation; hypersensitivity to EPL; congenital α-1 antitrypsin deficiency; other types of hepatitis; liver failure; severe organic gastrointestinal disorders; administration of medicines affecting liver function and not included in the standard treatment of the underlying disease within 1 month before screening; and other severe diseases.

All study participants were prescribed oral EPL paste 600 mg (ESSENTIALE®), one sachet thrice daily with meals (1800 mg/day) for 12 weeks, starting on day 1 of enrolment into the study. Additionally, participants were advised to follow their physician’s recommendations as part of their standard therapy for underlying liver disease (lifestyle changes for NAFLD, antiviral pharmacotherapy for viral hepatitis). All participants were advised to avoid alcohol consumption and implement dietary and physical exercise recommendations before study participation.

Citation: Kirill M Starostin, et al. “Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment”. EC Gastroenterology and Digestive System 7.5 (2020): 10-21.
Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment

Study outcomes

The primary outcome was occurrence of AEs associated with the use of the study drug (as per investigator judgment) during the 12-weeks treatment and 1-week follow-up periods. Secondary safety outcomes were the frequency (number and percent) of AEs not associated with the study drug, and serious AEs based on objective examination, patient interviews and analysis of their diaries (regardless of the causal relationship with the study drug) during 4, 8 and 12 weeks of treatment. Adherence to the prescribed treatment regimen was assessed after 4, 8 and 12 weeks. The following formula was used to estimate treatment adherence: \[ \text{Adherence} = \left( \frac{\text{number of sachets administered}}{\text{expected number of sachets administered}} \right) \times 100\%. \] A healthcare professional recorded all dosage changes and the number of missed doses (if any) in a registry. A result below 80% was interpreted as low adherence.

Patient-reported outcomes (clinical effectiveness) were assessed based on changes in overall clinical state, measured as intensity of any symptoms observed after 4, 8, and 12 weeks compared with baseline using a 7-point Global Overall Symptoms (GOS) score, in which 1 = “no problem” and 7 = “very serious problem which is impossible to ignore and impairs daily activities” [32]. An improvement of ≥ 30% from baseline on the GOS scale after 12 weeks of treatment was expected. The intensity of six gastrointestinal symptoms was also analyzed on a Gastrointestinal Symptoms (GIS) score. For this purpose, a questionnaire adapted from Veldhuyzen 2006 [32] and Svedlund 1988 [33] was used to measure the intensity of gastrointestinal symptoms on a 7-point Likert scale. The following six symptoms were assessed: fatigue; abdominal pain/discomfort; discomfort after meals; sensation of fullness after meals; nausea/vomiting; and eructation/bloating. The overall GIS score and the intensity of each of the six gastrointestinal symptoms were assessed separately. The proportion of patients with response to therapy (defined as a reduction in the GOS score to 0 or 1 - 2 points) was calculated. A response rate of ≥50% was expected.

Statistical analysis

Descriptive statistics were used for the statistical analysis of demographic data as well as the safety and patient-reported outcomes (effectiveness) variables. The descriptive analysis included calculation of N, means, standard deviations (SD), medians, Q1 and Q3 quartiles, and minimum and maximum values. The distribution of the variables was tested for normality using the Shapiro-Wilk test and skewness and kurtosis test; the homogeneity of variances was estimated using the Levene test (critical significance level \( P = 0.05 \)). For the comparison between time points, the ANOVA method was used (or the Kruskal-Wallis test in the case of nonparametric distribution), followed by a comparison based on Student’s t-test (or the Mann-Whitney U test, respectively), if necessary and paired Student’s t-test (or Wilcoxon signed-rank test, respectively). Statistical analysis was performed using SAS 9.4 (or above) and NCSS 10.0 (or above) software. The critical level of significance was \( P = 0.05 \) and the Bonferroni correction was used for multiple comparisons.

Assuming that the incidence of treatment-related AEs would be about 3.5% of the calculated sample size, an estimated 140 study participants (patients) were needed to achieve 80% power when comparing the proportion of patients with study drug-related AEs, based on Fisher’s Exact test with two-sided \( \alpha = 5\% \) (compared with a theoretical predetermined 10% incidence). Considering a 5% potential dropout rate, 147 participants were to be included in the study.

The safety analysis was conducted in the intention-to-treat (ITT) population (defined as study participants who received ≥ 1 dose of the study drug), while the effectiveness analysis was conducted in the per-protocol (PP) population (defined as study participants who completed all study procedures in accordance with the protocol). Adherence to the prescribed regimen was analyzed in a modified ITT (mITT) analysis that included all patients with available data, following a predetermined formula.

Results

Baseline characteristics

In total, 147 patients were screened and included in the study between August 31, 2015 and June 15, 2016. The ITT population analysis included 147 patients (mean ± SD age 44.8 ± 10.5 years) who received ≥ 1 dose of the study drug; 48.3% were male. Five major protocol deviations were recorded; four cases related to screening procedures at Visit 2, specifically assessing exclusion criteria based on a laboratory analysis conducted more than 30 days previously. The other major protocol deviation was a failure to meet one of the inclusion criteria [viral hepatitis was confirmed, but alanine aminotransferase (ALT) levels were not elevated], which was reported after inclusion and dispensing of the study drug. This patient discontinued the study and was excluded from the PP analysis. In total, four patients did not complete the study; two discontinued due to the unpleasant taste of the study drug, one discontinued for logistical reasons, and one

Citation: Kirill M Starostin, et al. “Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment”. EC Gastroenterology and Digestive System 7.5 (2020): 10-21.
was excluded due to failure to meet inclusion criteria (see protocol deviation described above). Thus, 143 patients (97.3%) completed the entire course of therapy and were included in the PP population.

Of the 147 patients in the ITT population, 107 (72.8%) had NAFLD and 41 (27.9%) had viral hepatitis; most of these patients had HBV, with one patient having concurrent HBV and HCV, and another patient having concurrent NAFLD and HCV. At baseline, most patients (n = 105; 73.5%) rated their overall condition as moderate or moderately severe, and only 12 patients (8.4%) reported no issues or overall minimal symptoms. Of the individual gastrointestinal symptoms, the most pronounced were fatigue (mean ± SD score 3.8 ± 1.51), abdominal pain and discomfort (3.72 ± 1.32), eructation, and bloating (3.65 ± 1.46).

At baseline, the most frequent comorbidities were hepatobiliary disorders (77.6%), metabolism and nutrition disorders (38.8%), infections (36.1%), gastrointestinal disorders (31.3%) and cardiovascular disorders (30.6%). In total, 82 patients (55.8%) were receiving concomitant medications for comorbidities.

Safety

During the 12-week treatment and 1-week follow-up periods, 37 drug-related AEs were observed in 22 patients (15.0%). Drug-related AEs primarily included diarrhea (16 cases in 10 patients [6.8%]) and dyspepsia (7 cases in 5 patients [3.4%]). Six cases of dyspepsia were observed during the 12-week treatment period and 1 case was observed during the 1-week follow-up period. The incidence of all other study drug-related AEs did not exceed 2% (nausea [2.0%], dysgeusia [2.0%], dry mouth [0.7%], thirst [0.7%] and abdominal pain [0.7%]). None of the participants discontinued treatment due to AEs and no deaths or other SAEs occurred.

Effectiveness and patient-reported outcomes

GOS score and response rate

At baseline, the mean ± SD GOS score was 4.21 ± 1.09. After 4 weeks of treatment, a significant reduction from baseline in mean ± SD GOS score to 3.01 ± 1.11 points (P < 0.01) was observed (i.e. a 28.4% reduction from baseline). This statistically significant reduction remained consistent during the entire treatment period, with a 43.7% reduction from baseline at 8 weeks (mean ± SD GOS score 2.37 ± 0.87 points; P < 0.01) and a 55.5% reduction from baseline after the full 12-week treatment period (mean ± SD GOS score 1.87 ± 0.91; P < 0.01; Figure 1). After the completion of the 12-week treatment period, the response rate was 81.1%, which exceeded the pre-established threshold of 50% (Figure 1).

Citation: Kirill M Starostin, et al. "Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment". EC Gastroenterology and Digestive System 7.5 (2020): 10-21.
GIS score

EPL paste therapy was associated with significant reductions in the severity of gastrointestinal symptoms, with statistically significant reductions from baseline in mean GIS scores observed after 4, 8 and 12 weeks of treatment (Figure 2). The mean GIS score decreased by 54.3% ($P < 0.01$) after 12 weeks of treatment, which exceeded the expected reduction of ≥ 30% (Figure 2A and 2B).

Figure 2: (a) GIS scores as assessed on a 7-point Likert scale. (b) Absolute and relative decrease in mean GIS score after 12 weeks of treatment (54.3%; $P < 0.01$), which met the expected threshold of ≥ 30% reduction.

Mean ± SD GIS scores decreased from 19.91 ± 5.74 at baseline to 14.48 ± 4.69 at 4 weeks ($P < 0.01$), 11.17 ± 3.57 at 8 weeks ($P < 0.01$), and 9.09 ± 3.55 at 12 weeks ($P < 0.01$). When considering the individual components of the GIS score, a significant reduction in each symptom intensity was observed after 4 weeks of treatment and remained significant at 8 and 12 weeks (Table 1).

<table>
<thead>
<tr>
<th>Gastrointestinal symptom</th>
<th>Mean ± SD score (% reduction vs baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.8 ± 1.51 (NA)</td>
</tr>
<tr>
<td>Abdominal pain/discomfort</td>
<td>3.72 ± 1.32 (NA)</td>
</tr>
<tr>
<td>Eructation/bloating</td>
<td>3.65 ± 1.48 (NA)</td>
</tr>
<tr>
<td>Sensation of fullness after meals</td>
<td>3.45 ± 1.42 (NA)</td>
</tr>
<tr>
<td>Early satiety</td>
<td>3.01 ± 1.45 (NA)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2.28 ± 1.34 (NA)</td>
</tr>
</tbody>
</table>

Table 1: Individual GIS scores at baseline and after 4, 8, and 12 weeks of treatment.

*p value < 0.01 vs baseline, Wilcoxon signed-rank test.

Citation: Kirill M Starostin., et al. “Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment”. EC Gastroenterology and Digestive System 7.5 (2020): 10-21.
Adherence to treatment

Two patients discontinued the study before Visit 3 (Week 4) with no data regarding administered dosages; therefore, 145 patients were included in the mITT analysis of treatment adherence at Visits 3 and 4 (Weeks 4 and 8) and adherence data were available for 143 subjects at Visit 5 (Week 12). At each visit, treatment adherence was calculated as 99%, meaning that almost all patients received ≥80% of the prescribed treatment as per the study protocol.

Discussion

Our study showed that the new paste formulation of EPL has a favorable safety profile in patients with NAFLD or viral hepatitis when administered as one dose thrice daily with meals over 12 weeks. The AEs specifically associated with the EPL paste formulation were bitter taste, dyspepsia and dry mouth. However, the investigators recognized these events as transient and not requiring treatment withdrawal. The EPL paste formulation was associated with statistically significant improvements from baseline in gastrointestinal symptom severity within the first 4 weeks of treatment that were maintained throughout the 12-week treatment period. The EPL 600 mg paste was also associated with a high level of treatment adherence.

The severity of gastrointestinal symptoms is known to significantly impact health and quality of life [34]. One of the quickest and easiest ways to assess a patient’s well-being is with validated questionnaires [33], which can help to assess the patient’s health condition as well as their health-related quality of life. In this study, the assessment of symptoms was made using GOS and GIS scores based on a 7-point Likert scale, which allowed for a more accurate assessment of the symptoms than the standard 4-point scale. This method for determining the severity of symptoms was based on the correlation of NAFLD progression with symptoms of impaired gastrointestinal function [35]. The GOS and GIS scores showed an improvement in overall gastrointestinal symptom severity within the first month of therapy that was sustained during the entire 12-week treatment period. This observation is consistent with a previous study, which reported a statistically significant and reliable improvement of biochemical blood parameters (fasting glucose, lipid profile, bilirubin and several serum enzymes) by the 30th day of treatment with PCH [36]. Similarly, most publications have observed an effect of EPL on steatosis after 3 - 6 months of treatment [14-18]. According to the available literature, the physical and mental dimensions of quality of life in patients with NAFLD are lower than those in the general population [37]. Considering these data and the fact that therapy with EPL reduces the level of steatosis and the intensity of clinical symptoms [14-18,36], we may assume that this treatment intervention may also improve health-related quality of life in patients with NAFLD. Further well-designed randomized controlled trials, including patient-reported outcomes are needed to confirm this hypothesis.

The diagnosis and treatment of NAFLD, as well as understanding its clinical importance, poses certain challenges for the clinician [5]. One of the reasons for this may be that it is mistakenly thought that NAFLD does not require any specific treatment. Moreover, often this condition does not result in significant patient burden. Clinical diagnosis of NAFLD is difficult, although thorough physical examination may detect liver enlargement through percussion and, although less probable, changes in the liver margin and consistency through deep palpation. However, in the context of the limited time available for ambulatory health consultations, this examination is mostly unattainable. As the symptoms of NAFLD are usually non-specific, reliable assessment of the liver structure requires instrumental diagnostic methods, which are not always available and have to be justified. Monitoring of the evolution of the disease is challenging as steatohepatitis can have no manifestations, being associated only with an asymptomatic increase in the blood transaminase activity. Due to the liver’s capacity for functional compensation, fibrotic changes do not result in any changes in its synthetic ability for some time. Lastly, no molecule has so far been proven effective for improving clinical outcomes in NAFLD patients in phase III clinical studies.

NAFLD, which is painless and difficult to diagnose and treat, increases the risk of cardiovascular death by up to three times [6,38]. NAFLD is also an independent risk factor for metabolic syndrome and diabetes, and a risk factor for colorectal cancer in men, breast cancer in women, and hepatocellular carcinoma regardless of sex [9].

Citation: Kirill M Starostin, et al. "Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment". EC Gastroenterology and Digestive System 7.5 (2020): 10-21.
This link between NAFLD and cardiovascular disease is comparable to the one that exists with dyslipidemia. In that instance, the connection between stroke/myocardial infarction and asymptomatic lipid abnormalities only became apparent almost a century after the initial research findings of Nikolai Annichkov in 1913, once multiple research studies, including the Framingham and Seven Countries studies, had been completed [39-41]. Throughout that century of research, clinicians were unsure about whether lipid profile tests were necessary. How could a 1 mmol/L change in low-density lipoprotein concentration be related to a catastrophic cardiovascular event? Today, this relationship is obvious.

The synthesis of lipoproteins and the regulation of fat metabolism generally takes place in the liver. Initially, triglyceride and cholesterol droplets accumulate in liver cells, confining fat metabolism abnormalities to the liver for the sake of the entire body. When this adaptive mechanism fails, the impaired fat metabolism within the liver spreads to the whole body, with potentially fatal consequences [42,43]. Therefore, it is clear how fatty liver may be linked to catastrophic cardiovascular events.

In recent years, a closer look at the symptoms of NAFLD has shown that this disease may manifest not only with fatigue, the sensation of heaviness in the upper right abdomen, and appetite changes. Patients with NAFLD may also present with concentration difficulties, memory difficulties, daytime drowsiness, mood changes, and emotional dysphoria [44-46]. Moreover, in addition to mood changes and depression which correlate with the intensity of hepatocyte degeneration and severity of liver damage [45], cognitive impairment is observed in “pure” steatosis. This cognitive impairment is unrelated to the hyperammonaemia-associated encephalopathy that occurs with decompensated liver cirrhosis [46].

With regard to selecting NAFLD treatment based on evidence-based medicine and keeping in mind that the first (benign and practically the only fully reversible) “hit” within the pathogenesis of NAFLD is steatosis, we provide the following conclusion. At the earliest stage of the NAFLD - the stage of steatosis - the patient should be encouraged to implement lifestyle modifications to become more physically active, switch to a healthy diet, and lose weight. However, knowing that patient adherence to non-pharmacologic therapies is often low, addition of pharmacotherapy with a proven effect on liver steatosis is recommended. As mentioned above, EPL have shown the best evidence for an effect on steatosis among existing hepatoprotective agents. The anti-steatosis effect of EPL is associated with reduced fatty acid synthesis in the liver, stimulated fatty acid beta-oxidation in hepatocytes, and correct packaging and secretion of very low-density lipoprotein [47-49]. There is also evidence that PCH affects the viability of mature adipocytes and inhibits the expression of certain genes, which may help to reduce fat mass [50]. The present study has shown the effect of EPL on the clinical state of the patients with NAFLD, including improving the severity of gastrointestinal symptoms. Since previous controlled studies showed a positive effect of EPL on the liver structure using objective diagnostic methods, including liver biopsy, the practical value of the present study is its assessment of the impact of EPL on patient-reported outcomes, which are gaining more importance in clinical practice [51].

Limitation of the Study

The limitations of this study include the absence of a control group and the absence of objective confirmation of changes in the liver structure following treatment. The strengths of this study include the use of patient-reported outcomes, which were not previously assessed in patients NAFLD receiving EPL. Another merit of the study is the safety assessment of an established drug in a new formulation. Finally, since the study sample included patients with NAFLD and chronic hepatitis, the use of EPL as an adjunctive therapy may improve the condition in both patient populations.

Conclusion

The study drug EPL paste 600 mg administered thrice daily with meals for 12 weeks in patients with NAFLD or viral hepatitis and gastrointestinal symptoms, showed a favorable safety profile (no serious AEs or deaths; most common AEs were diarrhea and dyspepsia). Beneficial patient reported outcomes of EPL paste was confirmed by the significant improvements in general symptoms and gastrointestinal symptoms, which were observed within the first 4 weeks of treatment and maintained at 8 and 12 weeks. Further confirmation of its

Citation: Kirill M Starostin, et al. “Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment”. EC Gastroenterology and Digestive System 7.5 (2020): 10-21.
clinical effectiveness was the high response rate (81.1%), which exceeded the 50% threshold established in the study protocol. Furthermore, the study drug showed high levels of treatment adherence. These findings indicate that EPL should be used as a first-line agent in patients with NAFLD in combination with non-pharmacologic therapies, the relevance and value of which should not be underestimated. The new dosage form of EPL may simplify administration in patients with swallowing difficulties, thereby potentially increasing patient adherence to treatment.

Acknowledgments

We are grateful to “Atlant Clinical Ltd.” for operational management of this trial, data management and statistical analysis. Also, we would like to thank Darya Osipova, MD and Kristina Kokoreva, MD, Sanofi Medical department specialists who helped us with medical writing and publication processing.

Conflicts of Interest

Kirill M. Starostin is an employee of Sanofi. Other authors declare no potential conflicts of interests.

Funding Statement

This clinical trial was sponsored by Sanofi.

Institutional Review Board Statement

This study was reviewed and approved by the Ethics Committee of the Ministry of Health of the Russian Federation [CHOLIL06301] № 20-2-466312/R/ET-Z from 01.12.2014.

Clinical Trial Registration

This study is registered on clinicaltrials.gov (NCT02517385).

Authors’ Contributions

Vladimir T. Ivashkin and Igor V. Maev were the national study coordinators who contributed to design of the study and supervised it. All authors participated in the acquisition, analysis, and interpretation of the data. Kirill M. Starostin contributed to the initial manuscript drafting and finalization. All authors have read and approved the final version of the manuscript.

Bibliography


Citation: Kirill M Starostin., et al. "Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment". *EC Gastroenterology and Digestive System* 7.5 (2020): 10-21.


Citation: Kirill M Starostin, et al. "Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment". EC Gastroenterology and Digestive System 7.5 (2020): 10-21.
Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment


*Citation*: Kirill M Starostin., et al. "Safety and Patient-Reported Outcomes in Non-Alcoholic Fatty Liver Disease and Viral Hepatitis Patients Taking Essential Phospholipids Paste as Adjunctive Treatment". *EC Gastroenterology and Digestive System* 7.5 (2020): 10-21.


