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Medication adherence to obeticholic acid: a real-world experience using medication event monitoring systems

Adherencia terapéutica de ácido obeticólico: experiencia real utilizando sistemas de monitorización de medicación electrónicos

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Abstract

Objective: We designed a clinical study to analyze patterns of adherence to obeticholic acid, factors influencing the adherence and potential correlation with treatment efficacy by using MEMS® cap in practice daily.
Method: A multicenter prospective observational study of patients with primary biliary cholangitis. Adherence will be measured by MEMS® cap, pill count, and patient-reported outcomes during 3 months. The quality of life will be self-reported using the Chronic Liver Disease Questionnaire test, European Quality of Life 5-Dimension Questionnaire test and Itch Severity Scale.
Conclusions: We expect to clarify if there is correlation between adherence with treatment efficacy and to identify causes for poor compliance and introduce measures to reduce its prevalence.

Resumen

Objetivo: Diseñamos un estudio clínico para analizar los patrones de adherencia al ácido obeticólico, los factores que influyen en la adherencia y la posible correlación con la eficacia del tratamiento mediante el uso de MEMS® cap en la práctica clínica diaria.
Método: Estudio observacional prospectivo multicéntrico de pacientes con colangitis biliar primaria. La adherencia se medirá mediante MEMS® cap, el recuento de comprimidos y se registrarán los resultados comunicados por el paciente durante 3 meses. La calidad de vida será autoinformada utilizando el Cuestionario de Enfermedad Hepática Crónica, el Cuestionario Europeo de Calidad de Vida en cinco dimensiones y la Escala de Intensidad del Picor.
Conclusiones: Esperamos identificar si existe una relación entre la adherencia con la efectividad del tratamiento e identificar las causas de la falta de adherencia para poder introducir medidas para reducir su prevalencia.

KEYWORDS
Medication adherence; Medication event monitoring systems; Obeticholic acid; Liver Cirrhosis, Biliary; Quality of life.

PALABRAS CLAVE
Adherencia a la medicación; Sistemas de monitorización de medicación electrónicos; Ácido obeticólico; Colangitis biliar primaria; Calidad de vida.

Introduction

Primary biliary cholangitis (PBC) is a rare autoimmune liver disease (prevalence of approximately 22.27 cases per 100,000 inhabitants in Europe) that predominantly affects middle-aged women[1]. This chronic autoimmune disease is characterized by elevated alkaline phosphatase (ALP) and γ-glutamyltransferase (GGT) levels due to inflammation, progressive non-suppurative destruction of interlobular bile ducts and collagen deposition within the liver[2].

Obeticholic acid (OCA) is the first selective Farnesoid X-receptor agonist approved for the treatment of patients with PBC with an inadequate response to therapy with ursodeoxyocholic acid (UDCA)[3].

Despite treatment of PBC has advanced lately and continues to evolve, we should bear in mind that the effectiveness of an oral therapy greatly depends on its adherence; otherwise, the rate of success may be compromised.

Adherence to treatment has been defined as the "extent to which patients take medications as prescribed by their health-care providers". The International Society for Pharmacoeconomics and Outcome Research defined adherence as the extent to which a patient acts following the prescribed interval and dose of a drug regimen[4,5].

The two definitions are subtly different, although both are usually calculated in practice as the percentage of doses taken correctly in an observation period.

In September 2010, a new taxonomy was introduced, in which adherence to medications is defined as the process by which patients take their medications as prescribed in the context of its three phases: initiation, implementation and discontinuation[6,7].

Related terms are compliance, defined as the "passive act of the patient to follow the provider's orders", and persistence, which is the length of time between initiation and the last dose, that immediately precedes discontinuation[5].

Depending on the drug and method of measurement, adherence rates range from 35% to 70%. Traditionally, self-reported questionnaires (SRQs), pill counts or analyses of pharmacy dispensing records are used to assess adherence, but these reports tend to overestimate adherence behavior[8,9].

As a result of technological advances to improve the measurement of medication adherence, the Medication Event Monitoring Systems (MEMS) are increasingly being recognized as the impactful and most objective adherence measurement strategy for many populations and research questions[9].

There is no ideal measurement, and all methods have limitations[10,11] but SRQs and MEMS operating together continue to emerge as the preferred effective method for measuring medication adherence[12].

Claxton *et al.*[13] published a systematic review of 76 studies in which compliance was measured with MEMS and suggested that drug regimen complexity is associated with a poor compliance. Moreover, a high percentage of patients discontinued treatment due to side effects and psychological factors like anxiety, depression and stress made it difficult to achieve adequate adherence.

It would be desirable to identify risk factors for poor adherence to influence them and apply intervention strategies to enhance medication compliance.

We have designed this study to analyze patterns of adherence to OCA for PBC, influencing factors and potential correlation between compliance with efficacy by using MEMS® cap in practice daily.

Methods

Objectives

Primary:

- To assess OCA therapy adherence in outpatients with PBC with inadequate response or unable to receive UDCA by MEMS® cap.
- To identify causes for poor compliance and introducing measures to reduce its prevalence.

Secondary:

- To evaluate the adherence of OCA 5 mg compared to OCA 10 mg in the cases of dose increase based on the safety and tolerability assessments during therapy.
- To assess the impact of OCA adherence in the absolute change in biomarkers of clinical outcomes [ALP, bilirubin, alanine transaminase (ALT)] at month 12. The proportion of subjects at month 12 with ALP < 1.67 upper limit of normal (ULN) and total bilirubin ≤ ULN and ALP decrease of ≥ 15% from baseline to month 12.
- To assess the impact of OCA adherence in the absolute change of non-invasive tests of liver fibrosis: Fibrosis-4 (FIB-4), aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) and transient elastography from baseline to month 12.
- To compare OCA adherence to the severity of liver fibrosis.
- To compare OCA adherence by social and economic factors.
- To assess the impact of OCA adherence in the absolute change in the Quality of life from baseline to month 3 in naive patients and during therapy in patients ongoing treatment.
- To assess OCA safety and tolerability from baseline to month 12 (5-10 mg).

Design

This is a prospective observational multicenter study of adherence in patients with PBC receiving OCA therapy due to inadequate response to UDCA or unable to tolerate UDCA (no UDCA for ≥ 3 months), to identify causes of non-compliance and characterize them better to introduce measures to reduce its prevalence. The study will begin in the last quarter of the year 2021 and will last 12 months. Adherence data will be collected prospectively during 3 months in the "implementation" phase of medication adherence to quantify the following variables: the proportion of prescribed drug taken, the proportion of days with the correct number of doses taken, the proportion of doses taken on time, in relation to the 24 hours time interval between successive doses, the distribution of inter-dose intervals and the longest interval between two doses.

Population

Eligibility criteria

The main inclusion criteria are:

- Patients aged ≥18 years.
- Patients with PBC:
  Definite or probable PBC diagnosis (consistent with American Association for the Study of Liver Disease and European Association for Study of the Liver Practice Guidelines) as demonstrated by the presence of ≥ 2 of the following three diagnostic factors:
  1. History of elevated ALP levels for at least 6 months.
  2. Positive antimitochondrial antibodies (AMA) titer or if AMA negative or in low titer (< 1:80) PBC specific antibodies (anti-GP210 and/or anti-SP100 and/or antibodies against the major M2 components [PDC-E2, 2-oxo-glutaric acid dehydrogenase complex]).
  3. Liver biopsy consistent with PBC.
- Patients receiving OCA therapy due to inadequate response UDCA (ALP ≥ 1.67 ULN or bilirubin > ULN but < 2 ULN treated with UDCA for ≥ 12 months) or unable to tolerate UDCA (no UDCA for ≥ 3 months).
- Ability to understand and follow related study instructions.
- Able to give informed consent.

Exclusion criteria:

- Other causes of liver diseases, including history of alcohol abuse during the previous year (defined as > 40 g/day in men and 20 g/day in women).
- Presence of clinical complications of PBC or clinically significant hepatic decompensation.

- History of liver transplantation, current placement on a liver transplant list or current Model for End-Stage Liver Disease score ≥ 15.
- Portal hypertension with complications, including known gastric or large esophageal varices, poorly controlled or diuretic resistant ascites, history of variceal bleeds or related therapeutic or prophylactic interventions or hepatic encephalopathy.
- Cirrhosis with complications, including history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma, bilirubin > 2 ULN.
- Hepatorenal syndrome (type I or II) or Screening serum creatinine > 2 mg/dL (178 µmol/L).
- Current or prior history of hepatocellular carcinoma.
- Subjects with human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS).
- Patients with severe pruritus or those requiring systemic treatment for pruritus.
- Subjects with mental incapacity, language barrier, insufficient social support or any other reason considered by the investigator precluding adequate understanding or cooperation in the study.
- History of malignancy including solid tumours and haematological disorders.
- Subjects with a significant extrahepatic disease that may impair short-term prognosis as well as the Chronic Liver Disease Questionnaire (CLDQ), such as congestive heart failure New York Heart Association Grade IV), chronic obstructive pulmonary disease GOLD > 3 or chronic kidney disease (serum creatinine > 3 mg/dL or under renal replacement therapy).
- Medical conditions that may cause nonhepatic increases in ALP or which may diminish life expectancy to < 2 years, including known cancers.

Intervention

Variables

- Collection of demographic data: sex, age, ethnicity, level of studies (primary, secondary, higher or university studies), employment situation (student, unemployed, retired or pensioner).
- Adherence: monitoring of the number and timing of pill taken will be assessed by a pill container that electronically records real-time information during each cap opening. MEMS® cap devices (Aardex, Ltd., Zug, Switzerland) will be used and the opening and closing times will be recorded in the medAmigo software (Aardex, Ltd.). All patients will be dispensed the exact medication for each cycle/visit.
  Also, the pharmacist validates the electronic data, pill count adherence index and assesses the self-reported adherence by some of the following questions such as: Do you think you have missed taking some pills since the last visit? When do you take the daily medication?
- Biochemistry and liver function: AST, ALT, ALP, bilirubin, GGT, albumin, prothrombin time, international normalized ratio, creatinine and others.
- Cardiovascular safety markers: lipoproteins (LDL, HDL, VLDL, ApoB, ApoA-1, ApoE, Lp[a]), total cholesterol, triglycerides.
- Immunoserological tests (AMA, antinuclear antibodies, antibodies against soluble liver or liver-pancreas, immunoglobulins IgG, IgA and IgM).
- Non-invasive assessments of liver disease evaluated by serum markers and imaging tests to calculate different noninvasive scores of liver fibrosis: a panel of non-invasive circulating fibrosis markers, APRI and FIB-4.
- Liver stiffness measurement (LSM) is assessed using the FibroScan® after overnight fasting and after a complete abdominal ultrasound examination. At least 10 measurements with an interquartile range/median ≤ 30% are used as reliability criteria.
- Clinical outcomes: Incidence of any of the following adjudicated events: death (for all causes), liver transplantation, chronic hepatitis C confirmed by two complementary imaging studies unless confirmed by biopsy, Model for End-Stage Liver Disease score ≥ 15, worsening of the Child-Pugh score at least 2 points, hospitalization (defined by an admission ≥ 24 hours) for bleeding from varicose veins, hepatic encephalopathy (defined by a score ≥ 2 from West Haven) or hepatic encephalopathy (confirmed by diagnostic paracentesis), ascites secondary to cirrhosis and requiring intervention (e.g., diuretics or paracentesis).
- Number of concomitant chronic medications.
- Measurement of health status: Hospitalization (reason, length of hospital admission, important medical procedures), visits to the Emergency Department, outpatient visits to the doctor.
- Safety and tolerability of adverse events: emerging treatment related adverse events, adverse events of special interest (including pruritus and liver safety), ECG, vital signs, pruritus and clinical laboratory evaluations (including changes in lipid profile).
- Questionnaires of quality of life and itching: CLDQ test, "European Quality of Life 5-Dimension Questionnaire" test (EQ-5D) and Itch Severity Scale.

Study procedures

Sample size and recruitment

Each participant will receive a MEMS® cap that records the date and time it is opened. The subjects for this study will be recruited in the Pharmacy Department. The Pharmacy Department manages patient adherence to the study and treatment compliance.

For an estimated population of 100 patients during the study period according to the following aspects: i) the recruitment time proposed by the research team; ii) recruitment taking place in all Galician hospitals; and iii) the number of patients to whom this drug is prescribed per year, taking into account an estimated rate of adherence to treatment of around 90% and assuming an alpha error of 5%, an accuracy of ± 5% would give us a sample size of at least 58 patients according to sample size calculation tables. Assuming a removal rate of 15%, we would have to include in the study a minimum population of 69 patients.

The data analysis will be performed after the data for the entire sample has been collected, using the SPSS Statistics® v.20.0 software package. The significance level is established at 0.05 and the limits of the confidence interval at 95%. A descriptive analysis of the baseline characteristics of the sample will be performed. The primary objective is to compare adherence (percentage of pills taken of those prescribed) between the responders (ALP ≤ 1.67 ULN and bilirubin ≤ ULN and ALP reduction by 15%) and non-responders. In case, the normality assumption holds, this will be tested by an independent sample t-test. In case of skewed distribution for adherence, the non-parametric Mann-Whitney test will be used instead. Logistic regression will also be used to identify possible confounders for adherence. Only the strongest predictors will be tested as confounding variables. Confounding variables are added as independent variables to the model relating response (dependent variable) to adherence (independent variable).

Ethical and legal aspects

The protocol was approved by the Drug Research Ethics Committee of Galicia (2019/600), and ethics committee approval for participation in a multi-centre study (April 2021). This study will be conducted according to the declaration of Helsinki and Good Clinical Practice. Written informed consent will be obtained from all patients before enrollment.

Discussion

To our knowledge, this is the first multicenter observational study to describe real-life medication adherence by MEMS in ambulatory patients with a rare disease. Another strength is the assessment of medication adherence using different methods.

Electronic reporting from microchip devices, such as MEMS® cap, is an attractive option and provides objective feedback about adherence to the health care professionals.

Other devices available are also considered the "gold standard" for adherence measurement[14], Med-eMonitor (InforMedix, Rockville, MD, USA), eCaps (Information Mediary Corporation, Ottawa, ON, Canada) and Medsignals (MedSignals Corporation, Lexington, KY) but we have chosen MEMS® cap as a key supplier because of our expertise with various clinical studies[15].

MEMS® cap can supply an automatic compilation of medication intake times (dosing history) providing a comprehensive characterization of adherence to medication. These statistics can provide information about which deviation from the prescribed medication regimen is sufficient to adversely influence the regimen's intended effect.

Various studies based on MEMS have shown that medication adherence is closely correlated with clinical outcome. For example, poor adherence to imatinib therapy was observed to be significantly associated with inadequate molecular response and less effective viral suppression in subjects with antiretroviral therapy[16,17]. In contrast, the results of a recently published study, showed that nonadherence to nilotinib or inadequate Cmin appeared not to be clinically relevant with respect to achieve an optimal response[18].

Recent meta-analyses investigated the effectiveness of electronic monitoring feedback to improve medication adherence and clinical outcomes[17,19,20]. However, most studies were based in various therapeutic areas (HIV, heart failure, hypertension or schizophrenia), different cut-off for adherence (the thresholds ranged from 67% to 95%, and in half of the studies, it was 80%), several outcome measurement and research with longer duration was lacking, making analysis difficult.

Nevertheless, to obtain more insight into factors related to the efficacy of treatment, the quality of life and side effects are studied in an exploratory manner. Especially, side effects may influence adherence, dose adjustments, and may thereby result in a reduced response.

The reduced quality of life and its causes may influence nonadherence, therefore, the examination of these factors will give a broad insight into the use of OCA from the patients "point of view". Since there is no ideal method in evaluating adherence, selecting at least various methods can give results that are closer to reality. However, the small sample size, observational study, short follow-up periods, inclusion of middle-aged adults, and Hawthorne effect can limit our findings. Nonetheless, we must also consider the complexity for analysis and difficulty interpreting of the results when using a multimeasure approach.

In conclusion, we expect that this study will provide valuable knowledge which will be useful for health care professionals to identify strategies for increasing adherence in their daily practice.

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Conflict of interests

No conflict of interests.

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