Reduction of cardiovascular events of Lomitapida versus Statins in patients with a diagnosis of familial hypercholesterolemia: A systematic review protocol.

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Abstract

Introduction: Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder that produces hypercholesterolemia and premature development of cardiovascular diseases. Statins are the drug of choice in these patients; however, a high percentage of patients cannot achieve their therapeutic goals with the maximum recommended doses, so Lomitapide may prove to be useful as a new treatment alternative to traditional statins.

Objective: The objective of this systematic review is to determine if Lomitapide is better than statins at reducing cardiovascular events in patients with a diagnosis of FH.

Methods: Randomized controlled trials (RCTs) and quasi-randomized trials of patients diagnosed with FH will be included. Primary outcome measures included several parameters: 1. Post-treatment low- and high-density lipoprotein (LDL and HDL, respectively) levels and 2. Presence of cardiovascular events. Electronic searches will be conducted in PUBMED, The Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and the scientific electronic library (Scielo). The assessment of the risk of bias will be used by the Cochrane tool. The measures of the treatment effect will be considered the mean differences (MD) and the 95% confidence intervals (CI). The evaluation of heterogeneity will be done by visual inspection of the funnel diagram. The evaluation of the quality of the evidence will be done using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Keywords: Lipoproteins, LDL; Hydroxymethylglutaryl CoA Reductases; Cardiovascular Diseases; Anticholesteremic Agents; Hypercholesterolemia; Cholesterol, LDL; Systematic Review; Protocols.

PROSPERO database record number (York University): CRD42020213807

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Introduction

Condition Description

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder that causes elevations in low-density lipoprotein (LDL) cholesterol [1], and these elevated LDL levels lead to the development of early atherosclerosis, resulting in the premature development of cardiovascular diseases and a short life expectancy [2].

Due to its dominant genetics, FH usually begins early in life with the establishment of high levels of LDL starting at birth [3]; however, its clinical debut varies according to its two inherited variants [4]. The homozygous variant generally debuts in the first decade of life with a very high risk of death from coronary heart disease before the age of 30. Since its two alleles have to be mutated, this variant is extremely rare with a prevalence of 1 case per million inhabitants who tend to have extremely high calculated LDL (LDL-C) levels between 800 and 1000 mg/dl; hence, these variants lead to greater cardiovascular risk [5, 6]. The heterozygous phenotype is the most common variant with a prevalence in the Caucasian population of 1 case per 500 inhabitants, which gives an approximate estimate of about 10 million affected in the world, the majority of whom (up to 80%) remain undiagnosed. LDL values are usually around 190 to 400 mg/dl, it has a later debut around 17 -to 25 years and presents earlier in the male sex. It has been noted that the clinical complications of atherosclerosis occur prematurely in men [5].

It is estimated that without treatment, approximately 50% of men with FH will suffer an episode of cardiovascular disease (CVD) before the age of 50 and 30% of women before the age of 60; hence, these findings emphasize the importance of early diagnosis and management of these patients. The main characteristic of the disease is the presence of exaggeratedly elevated LDL levels starting at birth and is also usually ac-companied by clinical signs, such as xanthomas and/or corneal arch [5, 6].

The etiology of FH is genetic due to mutations; thus, responsible loci exist. The most frequent and important is the LDL receptor gene (rLDL) located on the short arm of chromosome 19 followed by the apo B-100 gene on chromosome 2. To a lesser extent, defects in a transporter protein (PCSK 9) are responsible in addi-tion to forms of autosomal recessive hypercholesterol-emia, such as autosomal recessive familial hypercho-lesterolemia (HAR) due to mutations in the rLDL adapter protein and the very rare sitosterolemia characterized by increased absorption of cholesterol and deficient elimination of bile. Hence, new drugs have been developed whose therapeutic targets are these altered receptors [7].

Diagnosis is a real clinical challenge and is based on LDL levels (greater than 200mg/dl), family history of hypercholesterolemia in first-degree relatives, history of cardiovascular events at early ages, and the presence of xanthomas and a corneal arch. In Spain, the British Simon Broome and the criteria of the Dutch Lipid Clinic Network (RCLH) are used. These criteria have been validated via genetic diagnosis, which is considered the gold standard.

The clinical diagnosis is certain when the score is ≥ 8 and probability when the score is ≥ 6 [6]. The diagnosis of familial hypercholesterolemia in children is based on elevated levels of total cholesterol and LDL levels. In both children and adults, a genetic DNA study is performed if available [5].

In general, the treatment of FH is based on the adoption of hygienic–dietary measures and pharmacological treatment. The former are aimed at the adoption of healthy lifestyle habits through a diet low in saturated fats and rich in poly and monounsaturated fats, regular physical exercise, and abstinence from tobacco. Regarding pharmacological treatment, statins are considered the treatment of choice for this pathology. De-pending on the statins and the selected dose, LDL reductions between 25% and 58% can be achieved, thus reducing the risk of developing a cardiovascular event and therefore both mortality, however it has been seen that patients with high cardiovascular risk develop intolerance and in children its long-term safety is not firmly established, in addition, with the introduction of new drugs its efficacy has been diminished [4, 6].

Description of the Intervention

The focus on the pharmacological treatment of FH is based on the reduction of LDL levels, which can be achieved with the early introduction of statins, the drugs of choice. With respect to the age of onset in the

pediatric population, use of these drugs is recommended at 10 years in boys, after menarche in girls, and in adults, immediately after diagnosis. However, as previously mentioned, it has been seen that in the long-term, statins do not have a good safety profile and their efficacy is not as expected, which is why we com-pared them other another drug that was introduced in 2013. The importance of this drug lies in the beneficial effect that it is reported to have in reducing cardiovascular events and therefore in increasing survival [8].

This review compares these two drugs by evaluating the reduction in LDL cholesterol levels and risk of cardiovascular events and therefore also mortality.

1. LDL cholesterol levels are the predictor of cardiovascular risk in patients with FH, which makes it a useful measure to assess this risk.

2. Cardiovascular events represent an important cause of these premature events in FH patients, and the therapeutic efficacy of these drugs in reducing these events will be evaluated.

How the intervention works

This review will compare the efficacy of Lomitapide in reducing cardiovascular events in this type of pathology when compared with statins, which is the drug of choice in this pathology.

Thanks to its novel mechanism of action, Lomitapide produces a significant reduction not only in LDL cholesterol but also in total cholesterol and apolipoprotein B, thus constituting a new treatment strategy for this pathology.

Lomitapide was introduced in January 2013 as a new therapeutic approach for FH; however, a limitation in terms of the available bibliography about its great utility in clinical practice exists in addition to the great efficacy it shows at extremely low doses in reducing the LDL levels compared to extremely high doses of statins to achieve the same reductions. Many times, these statin doses are poorly tolerated.

A follow-up study was done in Italy in 2017 in which the electronic case reports of 52 patients with FH of autosomal recessive etiology (HAR) were examined. The mean follow-up age was 14.1 ± 7.3 years. Among these patients, high doses of statins and ezetimibe were recorded, and just over half of the patients were receiving

apheresis. Six of the patients (11.5%) had received Lomitapide. Compared with other lipid-lowering medications, patients receiving Lomitapide showed the greatest decreases in LDL-C levels despite discontinuing lipid apheresis. LDL-C levels were reduced by 88.3 ± 5.0 mg/dL compared to 62.0 ± 22.5% for statins plus ezetimibe and 70.6 ± 10.3% for the same regimen with added lipid apheresis. The research group commented that the use of Lomitapide in FH deserves further attention [9].

Therefore, with this intervention, all of the available information about this drug will be collected and an attempt will be made to demonstrate the efficacy of this drug over the gold standard in reducing LDL cholesterol levels and thus, decreasing of the risk of cardiovascular events in the long-term.

Why this review is important

As familial hypercholesterolemia is a not such a common disease and many of the times goes underdiagnosed. Since its diagnosis requires great expertise and clinical suspicion, its diagnosis is late, and many patients do not receive effective therapy until approaching the age at which important adverse cardiovascular events occur. Therein, lies the importance of receiving a timely and above all effective diagnosis.

In the search to find an effective drug from the beginning of treatment and that in the long-term reduces cardiovascular arteriosclerotic events, therefore leading to an increase in survival, the need for this review arose. Lomitapide, a novel drug, which has not been exploited enough in terms of its effectiveness in managing these patients will be evaluated in this review. A study in which the objective of our review is exemplified was carried out in 2017 by Leipold [10] that was precisely intended to measure the potential efficacy of Lomitapide on major adverse cardiovascular events (MACE) and survival. The results in terms of survival benefit analysis indicated that starting with Lomitapide at 18 years of age and reducing LDL cholesterol by 3.3 mmol/L from the start was shown to increase life expectancy by 11.2 years and delay the time to the first MACE by 5.7 years. The analysis suggested that lifetime Lomitapide treatment could increase mean life expectancy by 11.7 years and time to first MACE by 6.7 years.

Hence the importance of conducting a systematic search aimed at obtaining the greatest amount of data about this drug when compared with its standard treatment to demonstrate its benefits, especially in the long term, was demonstrated.

Objectives

To assess the reduction of cardiovascular events in patients with a diagnosis of FH treated with Lomitapide versus statins.

Methods

Eligibility criteria

Randomized and quasi-randomized clinical trials published in the last ten years were included. The study group will consist of patients with FH. Inclusion criteria will consist of selection of only those articles that are from reliable scientific sources that included patients with FH undergoing treatment with Lomitapide or statins. These articles should have included changes in LDL-C from baseline onwards and high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) changes after receiving treatment. These parameters are related to the reduction in cardiovascular events.

Type of study

Randomized controlled trials (RCTs) and quasi-randomized controlled trials will be included.

Types of participants

Patients with a diagnosis of FH based on the analysis of high TC and low HDL levels or based on genetic diagnosis or both will be included. Studies will be included regardless of the duration of the illness.

Articles that focus on patients in whom these two types of treatment are compared and in patients with pathologies other than FH will be excluded.

Types of interventions

Two main categories of interventions that will be tested in this review:

• Levels of HDL, LDL, and TC, measured before and after treatment; these are taken as predictive parameters of cardiovascular risk and therefore future cardiovascular events.

• Cardiovascular Events.

Types of outcome measures
Primary outcome measures

Studies will be included only if one or more of the outcomes listed below were measured or were intended to be measured.

1. Decreased levels of HDL, LDL, and TC post-treatment.

2. The presence or absence of cardiovascular events after study treatment.

Secondary outcomes

1. Health-related quality of life in a patient with coronary arthropathy was evaluated using a validated questionnaire, such as the Cardiovascular Limitations and Symptoms Profile (CLASP)

2. Less serious (mild) side effects, such as intolerance to treatment and/or mild allergic reactions.

3. Recurrence, reported as the number of cases that relapse after a successful resolution.

4. Adherence (compliance) to the assigned treatment.

5. Rating of satisfaction or improvement reported by the patient with the result.

We also reported the results of any cost-effectiveness analyses associated with the included trials.

Timing of Results Measurement

Outcome measures will be grouped into three different time periods: 1. short term (within one month of the intervention), 2. medium term (one month to six months) or 3. long term (more than six months).

Search methods for the identification of studies
Electronic searches

For this study, all of the studies or most of the studies that are available to the scientific community will be obtained from electronic searches carried out on Medline (Ovid Online), The Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and Scientific Electronic library (Scielo).

ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform for ongoing and recently completed trials will also be searched. No language restrictions applied.

In MEDLINE (Ovid Online), a topic-specific search strategy will be combined with the version that maximized the sensitivity of the highly sensitive Cochrane search strategy for identifying RCTs [11]. The search

strategies developed for CENTRAL and MEDLINE are reported in Table 1. These strategies will be modified for use in the other databases.

Searching for other resources
The reference lists of key trial reports and review articles will be manually searched. The corresponding authors of included studies and known investigators in the field of FH management will be contacted to help identify potentially relevant published and unpublished studies.

Data collection and analysis
Study selection
Ten authors independently selected the title and abstract from all search results. Full reports of potentially eligible studies will be retrieved, and study selection will be made by the same 10 authors under the guidance of a standardized eligibility form. Any disagreement will be resolved in consultation by an 11th author. If eligibility is still unclear, the study authors will be contacted for clarification.

Data extraction and management
Five review authors will independently extract the data according to the implementation of a standardized and tested data extraction form. Disagreements will be resolved by consensus when possible, but a sixth re-view author was consulted if a consensus cannot be reached. Data entry in Review Manager 2014 will be done by a reviewer.

Assessment of risk of bias in included studies
The assessment of the risk of bias in the included studies is based on the application of the Cochrane 'Risk of Bias tool [11]. Ten review authors independently reported on the following seven domains: 1. sequence generation, 2. allocation concealment, 3. blinding of participants and staff, 4. blinding of outcome assessment, 5. data integrity of outcome, 6. selective reporting of outcome data, and 7. any other relevant but unreported source of bias in the above domains. A separate assessment of risk of bias will be performed for blinding domains and incomplete outcome assessment will be performed for patient-reported, such as cardiovascular events) or objectively reported, such as number of outcomes, adverse events, and recurrence rate. The risk of bias classified for each domain is low,

unclear, or high. An eleventh review author will be consulted if a consensus cannot be reached.

Valid ways to blind the participant to most of the physical interventions used in the treatment of familial hypercholesterolemia will be used. Evidence from the assessment of successful blinding of participants will be required to rate a low risk of bias in the section "blinding of participants and staff". Incomplete outcome assessment (due to attrition or exclusions) will be considered as high risk of bias if an intention-to-treat protocol had not been used.

Table 1 MESH terms for the clinical studies search strategy.

Search	Main MESH term	Entry Terms (MESH)
1	Hyperlipoproteinemia Type I	[OR] Apolipoprotein C-II Deficiency [OR] Burger-Grutz Syndrome [OR] C-II Anapolipoproteinemia [OR] Chylomicronemia, Familial [OR] Familial Fat-Induced Hypertriglyceridemia [OR] Familial Hyperchylomicronemia [OR] Familial Hyperlipoproteinemia Type 1 [OR] Familial LPL Deficiency [OR] Familial Lipoprotein Lipase Deficiency [OR] Hyperchylomicronemia, Familial [OR] Hyperlipemia, Essential Familial [OR] Hyperlipemia, Idiopathic, Burger-Grutz Type [OR] Hyperlipoproteinemia Type Ia [OR] Hyperlipoproteinemia Type Ib [OR] Hyperlipoproteinemia, Type I [OR] Hyperlipoproteinemia, Type Ia [OR] Hyperlipoproteinemia, Type Ib [OR] LIPD Deficiency [OR] Lipase D Deficiency [OR] Lipoprotein Lipase Deficiency [OR] Lipoprotein Lipase Deficiency, Familial.
2	1 & Anticholesteremic Agents	[OR] Anticholesteremic Drugs [OR] Anticholesteremics [OR] Cholesterol Inhibitors [OR] Hypocholesteremic Agents [OR] Inhibitors, Cholesterol [OR] Lomitapide [OR] Juxtapid [OR] Lojuxta [OR] Hydroxymethylglutaryl-CoA Reductase Inhibitors [OR] HMG-CoA Reductase Inhibitor [OR] HMG-CoA Reductase Inhibitors [OR] Hydroxymethylglutaryl-CoA Reductase Inhibitor [OR] Inhibitors, HMG-CoA Reductase [OR] Inhibitors, Hydroxymethylglutaryl-CoA [OR] Inhibitors, Hydroxymethylglutaryl-Coenzyme A Statin [OR] Statins [OR] Statins, HMG-CoA
3	1 & Heart Disease Risk Factors	[OR] Cardiovascular Risk [OR] Cardiovascular Risk Factors [OR] Cardiovascular Risk Score [OR] Residual Cardiovascular Risk [OR] Risk Factors for Cardiovascular Disease [OR] Risk Factors for Heart Disease.

Measures of treatment effect

For continuous outcomes (such as cardiovascular events), mean differences (MD) and corresponding 95% confidence intervals (CI) will be used to measure treatment effects. When appropriate, final scores instead of changing scores will be used. Standardized mean differences (SMD) were used when different measurement scales are used; the final and change scores for SMDs are not to be grouped. The SMD will be translated back to a typical scale (for example 0 to 10 for cardiovascular events) by multiplying the SMD by a standard deviation between people (such as the standard deviation of the control group at the start of the trial).

For dichotomous outcomes such as adverse events, risk ratios (RR) and 95% CIs were calculated.

Unit of Analysis Problems

Unit of analysis problems may arise in studies that include participants with FH. When results are reported by feet and no adjustments are available, sensitivity analyses will be performed to assess the impact of including uncorrected data in the results. If the numbers with cardiovascular events were high, we first attempted to correct this issue by adjusting the effective sample size to take into account the fact that the participant and not the FH was treated as the randomized unit analysis. If this is not possible, the effects of excluding the trial from the pooled analyzes will be explored. Data from cross-over trials will be analyzed in the first time period to avoid sequencing or carry-over effects. Data presented at different time points within or between studies were grouped for presentation according to the length of follow-up: 1. short-term (less than four weeks), 2. medium-term (four weeks to less than six months) and 3. long-term (greater than or equal to six months). If studies with multiple arms will be identified, the relevant arms according to our protocol were included. When two comparisons with the same control group are combined in the same meta-analysis, the control group will be divided in half to avoid double counting.

Addressing missing data

We attempted to contact the trial authors for missing information and data. In cases in which it is possible, we will try to analyze available data using intention-to-treat principles. When possible, missing standard de-viations (SDs) from other statistics such as standard errors, confidence intervals, or P-values will be calculat-ed according to the methods recommended in the Cochrane Handbook for Systematic Reviews. of Interven-tions. Missing SDs from other sources will not be used. When possible, sensitivity analyses to explore the effects of missing binary data when they exceeded 10% of the trial population will be used.

Heterogeneity assessment

Statistical heterogeneity will be assessed by visual inspection of the forest plot and by taking into account the chi² statistic at a significance level of $P < 0.10$. The level of inconsistency between trials will be defined by the I² statistic and will be interpreted in the following manner: 1. 0% to 40% might not be important; 2. 30% to 60% may represent moderate heterogeneity; 3. 50% to 90% may represent substantial heterogeneity; and 4. 75% to 100% heterogeneity considerable [11].

Assessment of reporting biases

When a sufficient number of trials (more than 10 trials) contributed to the analysis of a primary outcome, a funnel plot was generated to explore possible small study biases. In interpreting funnel plots, the different possible reasons for funnel plot skewness were examined as described in section 10.4 of the Handbook [11].

To assess the reporting bias of the results, trial protocols will be compared with published reports. For studies published after January 1, 2010, the Clinical Trials Registry on the World Health Organization International Clinical Trials Registry Platform for the trial protocol will be examined. Cases in which it is evident that the results stated *a priori* (such as in a trial protocol) are not reported or reported selectively are indicated in the Risk of Bias table.

Data synthesis

Where appropriate, the results of comparable groups of trials will be combined using fixed-effect and random-effect models. The choice of the model to be reported was based on careful consideration of the degree of heterogeneity and whether this degree could be explained in addition to other factors, such as the number and size of the included studies. We will use the 95% CI at all times and consider not pooling data when considerable heterogeneity (I² > 75%) exists that

cannot be explained by the diversity of methodological or clinical characteristics between the trials. In cases in which it is not appropriate to pool the data, the trial data in the analyses or tables will still be presented for illustrative purposes and reported in the text.

Subgroup analysis and investigation of heterogeneity

Where data permitted, several subgroup analyses will be performed:

1. Age (under 18; 18 to 35; over 35 years old)
2. Gender
3. Body mass index ([BMI] ≤ 25 kg/m^2; > 25 kg/m^2)
4. Diagnosis of the disease (< 3 months; $\geq$ 3 months)
5. Level of physical activity (athletes or high levels of physical activity; non-athletes or sedentary).

The above subgroups will be analyzed at the main time points (less than one month, one month to less than six months, and six months or more) for each type of intervention.

We investigated whether the subgroup results will be significantly different by inspecting the overlap of CIs and performing the test for subgroup differences available in RevMan 2014 V.5.3 (Cochrane, Copenhagen, Denmark).

Sensitivity analysis

If sufficient data exist, sensitivity analyses on various aspects of the trial will be conducted and a review of the methodology will be done. Sensitivity analyzes will be explored:

1. the effects on primary outcomes of trial exclusion with high or unclear risk of selection bias (thus restricting the analysis to studies with low risk of selection bias due to the use of adequate methods of concealment of selection bias),
2. the effects of excluding trials reported only in conference proceedings or other brief reports,
3. the effects on primary outcomes of comparing studies with smaller sample sizes (less than 50 cases in each group) versus larger ones,
4. the effects of the lack of binary data, and
5. the choice of the statistical model to pool the data (fixed effects versus random effects).

Evidence quality assessment and Summary of Findings tables.

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be selected to assess the quality of the body of evidence for each outcome listed in types of outcome measures [12]. The high quality rating is reserved for a suite of RCT-based evidence. The quality rating will be downgraded to moderate, low, or very low depending on the presence and scope of five factors: 1. study limitations, 2. inconsistency of effect, 3. imprecision, 4. indirect evidence, and 5. publication bias.

When sufficient evidence is found, Summary of Findings tables will be prepared for each comparison using the available evidence for the three primary outcomes. The results will be presented during three established time periods (short-, medium-, and long-term).

Protocol corrections

To document future amendments to this protocol, the registry plan will use the PROSPERO Guide and update it in the selected database.

Final results

They will be published in a summarized version in the PROSPERO protocol and sent in full to an Indexed journal for the knowledge of the scientific community.

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Financing

Availability of data and materials

Does not apply.

Ethical statements

Not applicable for systematic reviews.

Protection of people

Not applicable for systematic reviews.

Data confidentiality

Not applicable for systematic reviews.

Publication consent

Not applicable for systematic reviews.

Conflicts of interest

Los autores declaran no tener conflictos de intereses. There is no sponsor or financial entity in this research.

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DOI: Digital Object Identifier
PMID: PubMeD Identifier
SU: Short URL

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