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[Intervention Protocol]

Pitavastatin for lowering lipids

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

Primary objective

To learn more about the pharmacology of pitavastatin by characterizing the dose-related effect and variability of the effect of pitavastatin on the surrogate marker: low-density lipoprotein (LDL cholesterol). The effects of statins on morbidity and mortality is not the objective of this systematic review.

Secondary objectives

To characterize the dose-related effect and variability of effect of pitavastatin on the surrogate markers: total cholesterol, high-density lipoprotein (HDL cholesterol), and triglycerides.

To quantify the effect of various doses of pitavastatin on withdrawals due to adverse effects.

BACKGROUND

Description of the condition

Cardiovascular disease is a major cause of death and disability in the developed world, accounting for more than one-third of total deaths (Kreatsoulas 2010). In the USA, cardiovascular disease causes one in three reported deaths each year (CDC 2011; Roger 2011). Existing evidence shows a weak association between adverse cardiovascular events and blood concentrations of low-density lipoprotein (LDL) cholesterol in adults (Grundy 2004). The current recommended treatment for secondary prevention of adverse cardiovascular events consists of diet and lifestyle changes plus drug therapy with the drug class widely known as 'statins'.

Description of the intervention

Pitavastatin is a new synthetic potent statin that received FDA approval in the USA in 2009. In a long-term trial pitavastatin has been shown to increase high-density lipoprotein (HDL) cholesterol in people with low HDL cholesterol levels < 40 mg/dL (Teramoto 2009). Pitavastatin is rapidly absorbed, reaching peak

plasma concentration within one hour and has a half-life of 11 hours. Pitavastatin is metabolized to a small degree by cytochromes P-450 2C8 and P-450 2C9 to 8-hydroxy-pitavastatin (M13) (Mukhtar 2005). Statins as a class have been shown in individual randomized controlled trials (RCTs) and systematic reviews of RCTs to reduce mortality and major vascular events in people with occlusive vascular disease (CTT 2005).

How the intervention might work

Pitavastatin acts in the liver by inhibiting an enzyme early in the pathway for cholesterol synthesis, 3-hydroxy-3-methyl-glutarylcoenzyme A reductase (HMG-CoA reductase). This enzyme irreversibly converts 3-hydroxy-3-methylglutaryl CoA to mevalonate (Moghadasian 1999). This reaction is the third step in a sequence of reactions resulting in the production of many compounds including cholesterol and its circulating blood derivatives, LDL cholesterol and very low-density (VLDL) cholesterol (Gaw 2000). The prevailing hypothesis is that statins reduce mortality and morbidity in patients with occlusive vascular disease by reducing liver production of cholesterol and thus causing a reduction in blood LDL cholesterol and a resulting decrease in atherogenesis. However, the HMG CoA reductase enzyme is also responsible for the production of ubiquinone (co-enzyme Q10), heme a, vitamin D, steroid hormones and many other compounds. It remains possible that the beneficial effects of statins are due to actions other than the reduction of cholesterol. These other actions have been referred to as the pleiotropic effects of statins (Liao 2005).

Why it is important to do this review

Statins are the most widely prescribed class of drugs in the world. Prescribing of statins is increasing, as are average prescribed doses. At the present time, clinicians have only an approximate sense of the different potency of the different statins. Previous systematic reviews have assessed the effect of statins on serum lipids (Bandolier 2004; Edwards 2003; Law 2003; Ward 2007). They have demonstrated that different statins have different potencies in terms of lipid lowering and that higher doses of statins cause greater lowering of serum lipids than lower doses (Kellick 1997; Schaefer 2004; Schectman 1996).

However, a systematic assessment of the potency, dose-response relationship, and variability of effect has only been published for atorvastatin (Adams 2015) and rosuvastatin (Adams 2014). This showed that rosuvastatin and atorvastatin are similar in the slope of the dose-response relationship but rosuvastatin is about three times more potent. The fluvastatin review is about to be submitted for publication (Adams 2016), and the cerivastatin review is in the protocol stage (Adams 2017). It is possible that, in addition to a difference in potency, the slope of the dose-response or the variability of response is different for pitavastatin. Statin-induced myopathy is common to all statins, and limits the use of statins in many patients. Knowledge of the effects of statins on blood lipids can help us to use them more effectively. We will use the percentage reduction from baseline on the following surrogate markers to describe the dose-response relationship of the effect of pitavastatin: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (Boekholdt 2012). We will use the results of this review to compare pitavastatin with rosuvastatin, atorvastatin, cerivastatin and fluvastatin. Subsequent reviews of other drugs in the class (i.e. lovastatin, pravastatin, simvastatin) will also be done, in order to compare the results of all the statins.

OBJECTIVES

Primary objective

To learn more about the pharmacology of pitavastatin by characterizing the dose-related effect and variability of the effect of pitavastatin on the surrogate marker: low-density lipoprotein (LDL cholesterol). The effects of statins on morbidity and mortality is not the objective of this systematic review.

Secondary objectives

To characterize the dose-related effect and variability of effect of pitavastatin on the surrogate markers: total cholesterol, high-density lipoprotein (HDL cholesterol), and triglycerides.

To quantify the effect of various doses of pitavastatin on withdrawals due to adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized placebo-controlled trials (RCTs) as well as uncontrolled before-and after-trials will be included. Before-and after-trials will be included, because it has been shown that there is no placebo effect of statins on lipid parameters and that a placebo control is therefore not essential (Tsang 2002). We will include cross-over trials if the outcomes are reported for the parallel arms prior to the cross-over.

Types of participants

Participants may be of any age, with and without evidence of cardiovascular disease. They can have normal lipid parameters or any type of hyperlipidemia or dyslipidemia. We will accept participants with various comorbid conditions, including type 2 diabetes mellitus, hypertension, metabolic syndrome, chronic renal failure or cardiovascular disease.

Types of interventions

Pitavastatin must be administered at a constant daily dose for a period of three to 12 weeks. We have chosen this administration time window to allow at least three weeks for a steady-state effect of pitavastatin to occur and to keep it short enough to minimize participants dropping out. We will include studies where pitavastatin is administered in the morning or evening or where it is not specified. Trials require a washout baseline dietary stabilization period of at least three weeks, where all previous lipid-altering medication is withdrawn. This baseline phase ensures participants follow a standard lipid-regulating diet and helps to stabilize baseline lipid values prior to treatment. In trials where participants were not receiving lipid-altering medications or dietary supplements before receiving the test drug, we will not require washout baseline dietary stabilization periods.
The control is a double-blind placebo in the RCTs.

Types of outcome measures

Primary outcomes

1. Placebo-controlled RCTs: Mean percentage change of LDL cholesterol from baseline of different doses of pitavastatin minus percentage change from baseline with placebo.
2. Before-and-after trials: Mean percentage change of LDL cholesterol from baseline of different doses of pitavastatin.

Secondary outcomes

1. Placebo-controlled RCTs: mean percentage change of total cholesterol from baseline of different doses of pitavastatin minus mean percentage change from baseline with placebo.
2. Before-and-after trials: mean percentage change from baseline of total cholesterol of different doses of pitavastatin. We recognize that effects on total cholesterol are primarily due to effects on LDL cholesterol, which is why this is a secondary outcome.
3. Placebo-controlled RCTs: mean percentage change of HDL cholesterol from baseline of different doses of pitavastatin minus mean percentage change from baseline with placebo.
4. Before-and-after trials: mean percentage change from baseline of HDL cholesterol of different doses of pitavastatin.
5. Placebo-controlled RCTs: mean percentage change of triglycerides from baseline of different doses of pitavastatin minus mean percentage change from baseline with placebo.
6. Before-and-after trials: mean percentage change from baseline of triglycerides of different doses of pitavastatin.
7. End of treatment variability (standard deviation (SD)) and coefficient of variation of LDL cholesterol measurements for each dose of pitavastatin. It is important to know whether pitavastatin has an effect on the variability of lipid measures and ultimately to compare this with the effect of other statins.
8. Placebo-controlled RCTs: Withdrawals due to adverse effects. This is an important measure of harm that can only be assessed in the placebo-controlled trials.

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist will search the following databases from date of inception for published, unpublished, and ongoing studies:
1. the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web);
2. MEDLINE Ovid (from 1946 onwards), MEDLINE Ovid Epub Ahead of Print, and MEDLINE Ovid In-Process & Other Non-Indexed Citations;
3. Embase Ovid (from 1974 onwards);
4. ClinicalTrials.gov (www.clinicaltrials.gov)
5. World Health Organization International Clinical Trials Registry Platform (www.who.it.trialsearch).

The subject strategies for databases will be modelled on the search strategy designed for MEDLINE in Appendix 1.

Searching other resources

1. The Cochrane Hypertension Information Specialist will search the Cochrane Database of Systematic Reviews (CDSR) via Wiley, the Database of Abstracts of Reviews of Effects (DARE) via Wiley, and Epistemonikos to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials.
2. We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.
3. We will contact experts/organizations in the field to obtain additional information on relevant trials.
4. We will contact original authors for clarification and further data if trial reports were unclear.

We will include grey literature by searching other resources.
1. ProQuest Dissertations and Theses (search.proquest.com/pqdtft/).

2. OpenTrial (opentrials.net).
3. US Food and Drug Administration (www.fda.gov/).
4. European Patent Office (worldwide.espacenet.com).

Data collection and analysis

Selection of studies

Initial selection of trials will involve retrieving and reading the titles and abstracts of each paper found from the electronic search databases or bibliographic citations. We will provide a PRISMA flow diagram. Two review authors (SA and NA) will analyze the full-text papers independently, to decide on the trials to be included. We will resolve disagreements by recourse to the third review author (JMW). Two review authors (SA and NA) will independently extract the appropriate data from each of the included trials. If there is disagreement over a value, we will reach consensus by data recalculation to determine the correct value.

Data extraction and management

We will directly extract the mean percentage change from the data or will calculate it from the baseline and endpoint values. We will add the calculated data to the 'Data and analyses' section of the review. If the calculated data differ from the given data by more than 10%, the data will not be included in the review. We will extract standard deviations (SDs) and standard errors (SEs) from the report or will calculate them when possible. We will enter data from placebo-controlled and uncontrolled before-and-after trials into Review Manager 5 (RevMan 2014) as continuous and generic inverse variance data, respectively.

Assessment of risk of bias in included studies

We will assess all trials using the Cochrane 'Risk of bias' tool under the categories of adequate sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential biases. We will produce 'Risk of bias' tables' as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 8 (Higgins 2011).

Measures of treatment effect

We will analyze the treatment effects as mean difference (MD) for each dose in the placebo-controlled RCTs and generic inverse variance for each dose in the before-and-after uncontrolled trials separately. In the event that the mean effects from the two trial designs are not statistically different, we will re-analyze all efficacy study data using the generic inverse variance to determine the overall weighted treatment effects and their 95% confidence intervals (CIs) for serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Unit of analysis issues

The unit of analysis will be the mean values for the people completing the trial for each trial. In the case of trials with multiple treatment arms with different doses of pitavastatin, we will correct the N value of the placebo group by dividing it by the number of comparisons.

Dealing with missing data

We expect follow-up to be reasonably high for these short-term trials. The data will however represent treatment efficacy and not real-world effectiveness of pitavastatin on these lipid parameters. When data are missing, we will request them from the authors. The most common type of value that is not reported is the SD of the change.

In the case of a missing SD for the change in lipid parameters, we will impute the SD using the following hierarchy (listed from high to low preference).

1. SD calculated either from the t statistics corresponding to the exact P value reported or from the 95% CI of the MD between treatment groups.
2. Average weighted SD of the change from other trials in the review (Furukawa 2006).

It is common for the SD to be miscalculated. Therefore in order not to overweight trials where it is inaccurately calculated and much lower than expected, we will use the imputed value by the method of Furukawa 2006 when SD values are less than 40% of the average weighted SDs.

Assessment of heterogeneity

The Chi^2 test to identify heterogeneity is not appropriate because it has low power when there are few studies but has excessive power to detect clinically unimportant heterogeneity when there are many studies. The I^2 is a better statistic. I^2 calculates between-study variance/(between study variance + within study variance). This measures the proportion of total variation in the estimate of the treatment effect that is due to heterogeneity between studies. This statistic is also independent of the number of studies in the analysis (Higgins 2002). We will explore the cause of heterogeneity when an I^2 is > 50%.

Assessment of reporting biases

We will assess publication bias using funnel plots, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 10 (Sterne 2011).

Data synthesis

We will enter all placebo-controlled studies into Review Manager 5 (RevMan 2014) as MD fixed-effect model data to determine the weighted treatment effect and 95% CIs for blood total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. We will enter all uncontrolled before-and-after studies as generic inverse variance fixed-effect model data to determine the weighted treatment effect. If the effect in the placebo-controlled trials is not statistically significantly different from the before-and-after trials, we will enter all trials for each dose as generic inverse variance to determine the best overall weighted treatment effect for each dose. If an I^2 is $\geq$ 50%, we will use the random-effects model to assess whether the pooled effect is statistically significant.

We will record trial data of each study and dose in GraphPad Prism 4, to yield a weighted least squares analysis based on the inverse of the square of the SE for each lipid parameter, to generate weighted log dose response curves. We will enter the number of participants in placebo-controlled trials, who prematurely withdrew due to at least one adverse effect in Review Manager 5 (RevMan 2014) as dichotomous data for each dose and all combined doses of pitavastatin and report it as RR versus placebo.

Data presentation - 'Summary of findings' tables

We will use the GRADE approach to assess the quality of the supporting evidence behind each estimate of treatment effect (Schünemann 2011a; Schünemann 2011b). We will present key findings of the review, including a summary of the amount of data, the magnitude of the effect size and the overall quality of the evidence, in a 'Summary of findings' table. We have preselected the primary outcome: LDL cholesterol lowering for efficacy of pitavastatin (by dose), and withdrawals due to adverse effects for all doses for harm.

Subgroup analysis and investigation of heterogeneity

The main subgroup analyses are the different doses of pitavastatin. We will assess heterogeneity using the I^2 (Higgins 2002). If an I^2 is $\geq$ 50%, we will attempt to identify possible causes for this by carrying out a number of planned subgroup analyses, provided there are sufficient numbers of trials (see below).

We will analyze subgroups based on the following factors.

1. Placebo-controlled trials versus before-and-after trials (described above).
2. Men versus women
3. Morning administration time versus evening administration time.
4. Drug industry funded versus non drug industry funded trials.
5. Twice daily versus single dose.

Sensitivity analysis

We will conduct sensitivity analyses to assess the effect of different co morbidities, such as familial hyperlipidemia, on the treatment effect.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update

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1 pitavastatin.mp. (674)

2 alipza.mp. (0)

3 itavastatin.mp. (6)

4 nisvastatin.mp. (8)

5 livalo.mp. (15)

6 livazo.mp. (2)

7 or/1-6 (674)

8 animals/ not (humans/ and animals/) (4328959)

9 7 not 8 (529)

10 remove duplicates from 9 (513)

CONTRIBUTIONS OF AUTHORS

JMW, NA and SPA contributed to the design of the protocol.

DECLARATIONS OF INTEREST

Stephen P Adams: None known.

Nima Alaei: None known.

James M Wright: None known.

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