A systematic review and meta-analysis on treatment non-adherence and non-persistence to intravitreal anti-vascular endothelial growth factor therapy

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Review question

1. What is the prevalence of non-adherence and non-persistence to intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy?

2. What are the barriers/reasons associated with non-adherence and non-persistence to anti-VEGF therapy? Are they the same in different disease states?

3. What are the strategies/interventions to tackle non-adherence and non-persistence to anti-VEGF therapy?

Searches

An electronic search of databases will be conducted for research articles published from the start of the databases until December 2020: PubMed, Embase, MEDLINE, CINAHL Plus (The Cumulative Index to Nursing and Allied Health Professionals), Scopus, Cochrane Library (The Cochrane Database for Systematic Reviews), PsycINFO, Web of Science and Google Scholar

Types of study to be included

There will be no restriction to study design regarding primary research articles (original research).

Condition or domain being studied

Anti-VEGF therapy non-adherence and non-persistence, barriers to adherence and persistence to medication and therapy follow up.

Participants/population

Inclusion: Patients treated with intravitreal Anti-VEGF therapy for ocular diseases (for example: AMD, diabetic retinopathy).

Exclusion: Patients not on intravitreal Anti-VEGF therapy, or treated with Anti-VEGF therapy but not for ocular conditions.

Intervention(s), exposure(s)

Intervention(s), exposures(s) Anti-VEGF therapy
Inclusion: Any study with patients on anti-VEGF therapy and ocular diseases which require anti-VEGF therapy. Patients receiving intravitreal injections such as with the following medications ranibizumab, Lucentis, aflibercept, Eylea, Zaltrap, Avastin, bevacizumab. Studies reporting rates of non-adherence and/or non-persistence to anti-VEGF therapy and studies including strategies/interventions to tackle non-adherence and/or non-persistence. Studies assessing reasons and barriers to non-adherence and non-persistence to anti-VEGF therapies and regimens. No eligibility restrictions will be placed based on the type of anti-VEGF used or the relevant ocular disease and the treatment regimen of anti-VEGF used.
Exclusion: Studies will be excluded if they are review or expert opinion articles, case studies and series. Where duplicate papers are identified, the research paper with the most completely reported data will be included. Studies not reporting outcomes such as non-adherence and non-persistence and studies not

reporting barriers to treatment with anti-VEGF medications and studies with patients receiving other intravitreal injections not anti-VEGF.

Comparator(s)/control
Not applicable

Main outcome(s)
Degree/prevalence of non-adherence and non-persistence to anti-VEGF therapy.

* Measures of effect

Rate and prevalence of non-adherence and non-persistence to anti-VEGF therapy.

Additional outcome(s)
Distinguish non-adherence and non-persistence by patient, physician and centre-related reasons, as well as intentional and non-intentional causes, investigate strategies/interventions to improve medication adherence and treatment follow up in patients on anti-VEGF therapy. Identify specific barriers associated with non-adherence to Anti-VEGF therapy.

* Measures of effect

Reasons and barriers, intentional and non-intentional non-adherence and non-persistence.

Data extraction (selection and coding)
The search will be done in two steps. Firstly, studies will be identified by initial screening of titles and abstract. Then full text screening will be done for the selected articles. The screening process will be carried out independently by two reviewers; any conflict regarding the selected articles will be resolved by consulting the third reviewer. A data extraction tool will be developed based on aims and objectives. The extraction parameters will be the study name, name of investigator, year of study, location, study design, source of data, study duration, population size, gender ratio, mean age, intervention and regimen, definition of non-adherence and non-persistence used, non-adherence by gender, overall non-adherence to anti-VEGF therapy, reasons/barriers for non-adherence and non-persistence, medication used, frequency of follow-up, participant population and disease type.

Risk of bias (quality) assessment
Since different types of studies will be included, the assessment will be carried out using the National Institute of Health (NIH) quality assessment tool. This will include assessment of quality around considering the risk of potential biases such as information bias, measurement bias or other confounding factors. The process will be undertaken by two reviewers independently, with any disagreements resolved by consensus. For RCTs we will use Cochrane risk-of-bias tool for randomized trials.

Strategy for data synthesis
Narrative synthesis of the quantitative data along with thematic data synthesis of the qualitative data will be done. The synthesis process will be carried out in three stages. The quantitative and the qualitative synthesis will be carried out in parallel and then third synthesis where combining the results of the two previous synthesis will take place.

Meta-analysis will be performed on eligible studies included in this review. For outcomes including prevalence/rate of non-adherence and non-persistence.

Meta-analysis for prevalence of non-adherence and non-persistence:

Pooled prevalence of non-adherence non-persistence along with their 95% Confidence Intervals will be estimated using random effects models. The results will be presented using forest plots. Heterogeneity among the studies will be described using I^2 statistics along with $?^2$ test 95% prediction intervals will also be presented to show the variability of the pooled estimates. P value level < 0.05 will be considered as the level of statistical significance. The random effects method will be used to measure the heterogeneity level. Measuring I^2 value and 95% Confidence Interval will show statistical heterogeneity. If there is sufficient homogeneity across included studies, forest plots and the meta-analyses will be created using RevMan®.

Factors/reasons/barriers associated with non-adherence will be analysed using World Health Organization's multidimensional adherence model (MAM). We will categorise factors associated with non-adherence according to the five domains of the MAM which are: 1) socioeconomic factors, 2) health care system-related factors, 3) condition-related factors, 4) treatment-related factors, and 5) patient-related factors.

Analysis of subgroups or subsets
Sub-group analyses will also be undertaken if eligible studies are found for example for different disease states (for example: as AMD, diabetic retinopathy, myopia maculopathy).

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Type and method of review
Meta-analysis, Systematic review

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28 October 2020

Anticipated completion date
15 February 2021

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None

Conflicts of interest

Language
English

Country
England

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Humans; Intravitreal Injections; Vascular Endothelial Growth Factors

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06 November 2020

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25 October 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
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