Review Article

The methodological quality of systematic reviews comparing intravitreal bevacizumab and alternates for neovascular age related macular degeneration: A systematic review of reviews

Pradeep Paul George, Joseph Antonio DeCastro Molina, Bee Hoon Heng

Objective: To systematically collate and evaluate the evidence from recent SRs of bevacizumab for neo-vascular age related macular degeneration. **Materials and Methods:** Literature searches were carried out in Medline, Embase, Cochrane databases for all systematic reviews (SRs) on the effectiveness of bevacizumab for neo-vascular age related macular degeneration, published between 2000 and 2013. Titles and abstracts were assessed against the inclusion/exclusion criteria using Joanna Briggs Institute (JBI) study eligibility form. Data was extracted using the JBI data extraction form. The quality of the SRs was assessed using JBI critical appraisal checklist for SRs. Decisions on study eligibility and quality were made by two reviewers; any disagreements were resolved by discussion. **Results:** Nine relevant reviews were identified from 30 citations, of which 5 reviews fulfilled the review's inclusion criteria. All 5 reviews showed bevacizumab to be effective for neovascular AMD in the short-term when used alone or in combination with PDT or Pegaptanib. The average quality score of the reviews was 7; 95% confidence interval 6.2 to 7.8 (maximum possible quality score is 10). The selection and publication bias were not addressed in all included reviews. Three-fifth of the reviews had a quality score of 7 or lower, these reviews had some methodological limitations, search strategies were only identified in 2 (40%) reviews, independent study selection and quality assessment of included studies (4 (80%)) were infrequently performed. **Conclusion:** Overall, the reviews on the effectiveness of intravitreal/systemic bevacizumab for neovascular age-related macular generation (AMD) received good JBI quality scores (mean score = 7.0 points), with a few exceptions. The study also highlights the suboptimal reporting of SRs on this topic. Reviews with poor methodology may limit the validity of the reported results; hence efforts should be made to improve the design, reporting and publication of SRs across all journals.

Key words: Bevacizumab, intravitreal, neovascular age related macular degeneration, systemic, systematic review, systematic review of reviews

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Age-related macular degeneration (AMD) is a progressive chronic disease of the central retina and the leading cause of blindness in elderly people worldwide; including Singapore.[1-14] With increasing life expectancy, the worldwide prevalence of AMD is set to increase. Neovascular AMD is characterized by abnormal growth of new blood vessels under the macula, it accounts for only 20% of the cases with AMD, but responsible for 90% of the cases of legal blindness.[5]

Over the past decade, there have been a variety of medical therapies introduced with variable success to treat the neovascular form of AMD. Recently, the anti-vascular endothelial growth factors (VEGF) pegaptanib and ranibizumab became available for the treatment of exudative AMD.[6-10] In contrast to pegaptanib, intravitreal injections with ranibizumab led to a significant vision improvement. In fact, ranibizumab was the first drug to improve vision in exudative AMD, compared to interventions used earlier which only delayed progression.[6,7] Major disadvantages of this intervention are the costs and the need to give intravitreal injections repeatedly. Bevacizumab which is closely related to ranibizumab is derived from the same parent murine monoclonal anti-body as ranibizumab and is an off-label drug used for neovascular AMD. Interestingly both these drugs are from the same biotech company, which is not willing to approve bevacizumab for exudative AMD, as doing so would jeopardize its market for ranibizumab, which is the approved drug for the condition.

Bevacizumab was originally approved for the treatment of colon cancer but not for the treatment of AMD. A major advantage of bevacizumab is its price, which is about 1-5% the price of ranibizumab. Mainly for this reason, it is now used worldwide and on a large-scale off-label for the treatment of exudative AMD.

Medical and public health decisions are informed by systematic reviews, which make the quality of reviews an important scientific concern. Evidence from observational studies and few randomized clinical trials (RCT's) suggest that off-label bevacizumab is effective for the treatment of exudative AMD. However, evidence from systematic reviews on the effectiveness of bevacizumab for AMD is equivocal, with some systematic reviews in favor of intravitreal bevacizumab while some are not. This sets the stage for critical appraisal of quality of systematic reviews on intravitreal bevacizumab for neovascular age related macular degeneration.

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Materials and Methods

We adopted a 'review of reviews' approach as proposed by the Health Development Agency (HDA):[9] Given the increasing number of systematic reviews of interventions in ophthalmology literature,[10] the goal of this systematic review of reviews is to collate the evidence and appraise the quality of evidence from published reviews on intravitreal bevacizumab for neovascular AMD.

Inclusion and exclusion criteria

We searched the literature for published systematic reviews (and meta-analyses) of observational and experimental studies whose primary purpose was to ascertain the effectiveness of intravitreal bevacizumab for neovascular AMD. Reviews which looked at patients with neo-vascular AMD regardless of the stage/severity of disease or with subfoveal choroidal neovascularization (CNV) secondary to neovascular AMD were included. The intervention of interest in the review was intravitreal bevacizumab compared against photodynamic therapy (PDT) with Verterporfin, Pegaptanib or Ranibizumab. Reviews which were not labeled as systematic but included an explicit statement of search methods, inclusion, exclusion, data synthesis were included as well. The primary outcome of interest for the review was improvements in visual acuity (VA) measured by Snellen or ETDRS charts and decrease in central retinal thickness (CRT). All types of primary studies (observational and experimental) were excluded; similarly reviews which depended upon previous systematic reviews for their primary data were excluded.

Search Strategy

We conducted searches in three databases Medline (via PubMed), EMBASE, Cochrane Library and Centre for Reviews and Dissemination (CRD) databases for systematic reviews published between 2000 and 2013. The following are free text keywords used "Macula*" or "AMD" or "ARMD" or "intra (-) vitreous" or "intra-vitreal" in any field, and for the intervention the search terms are "bevacizumab" or "avastin" in any field. The following mesh terms were also searched in combination with the above free text keywords, (("Intravitreal Injections"[Mesh] OR "Injections, Intravenous"[Mesh]) AND "bevacizumab "[Substance Name]) AND "Wet Macular Degeneration"[Mesh] AND ("humans"[MeSH Terms] AND (Meta-Analysis[ptyp] OR Review[ptyp])). The search was restricted to English language publications and systematic reviews. Search for unpublished systematic reviews included searches conducted in ProQuest Dissertations and Thesis, Conference Proceedings and Mednar.

Review selection and critical appraisal

Titles and abstracts of identified reviews were examined independently by 2 reviewers to assess each review for inclusion using Joanna Briggs Institute (JBI) study eligibility form (Appendix I). Data from eligible reviews was extracted using the JBI data extraction form (Appendix II). The quality of the systematic reviews was assessed using JBI critical appraisal checklist (Appendix III) for systematic reviews which looks at 10 critical aspects of the systematic review. Scores were given for adherence to each of those aspects, A minimum score of 1 and a maximum score of 10 would signify a well conducted SR. Decisions regarding study eligibility and quality were made by two reviewers, any disagreements were resolved by discussion.

Data extraction and synthesis

Information on primary studies was extracted from the reviews; in the case where reviews reported discrepant study findings, the primary studies were consulted. Information on the reviewers' assessment of the evidence, design and findings of relevant primary studies were extracted from each review. The level of evidence in support of (or discounting) the effect of an intervention was classified as: 'sufficient';' tentative'; 'insufficient'; or 'no' evidence from reviews. These were derived using a framework [Table 1] based on the quality of the reviews, the reviewers' conclusions and the designs/findings of the primary studies included in the reviews.[11] In the absence of controlled trials, longitudinal cohort and case–control designs (involving incident cases) were considered to be more 'robust', whereas ecological, serial cross-sectional and cross-sectional designs were considered to be 'weaker'.

Results

Nine relevant reviews were identified from over 30 citations, of which 5 reviews fulfilled the review's inclusion criteria. The following were the reasons for excluding 4 reviews: Studies primarily looked at the safety of bevacizumab without focusing on its effectiveness (2), the major criteria for quality appraisal were not satisfactorily fulfilled (2), (search sources inadequate, criteria for critical appraisal inappropriate, critical appraisal not done independently, data extraction not independently done, methods used for combining studies were inappropriate). Table 2 shows the included and excluded studies with their corresponding JBI quality score.

Quality of studies included in the reviews

The 5 included reviews were published between 2009 and 2012; they summarized 126 publications (after excluding duplicate publications) on intravitreal bevacizumab for neovascular age related macular degeneration. 19% of these publications were prospective studies and 10% of these were randomized controlled trials (RCTs) and the rest had designs with no control group which includes case series and before-after studies.

The review question was clearly stated in all included reviews either in the title, abstract or in text. The average quality score of the reviews was 7 (95% confidence interval 6.2 to 7.8); maximum possible quality score is 10 [Table 3]. Publication bias was not addressed in all included reviews. Three-fifth of the reviews had a quality score of 7 or lower, these reviews had some methodological limitations. The search strategy was appropriate only in 40% of the reviews. The sources of studies and inclusion criteria were appropriate for 60% of the reviews. Criteria for appraisal were appropriate and independent appraisal was conducted in most of the reviews. Methods used to minimize error in data extraction were not specified in most of the reviews [Table 4]. Three out of the five reviews searched 2 or more databases. Data were tabulated as narrative summaries due to the heterogeneity of the design and the findings [Table 5].

All 5 reviews showed bevacizumab to be effective for neovascular AMD in the short-term when used alone or in combination with PDT or Pegaptanib. Table 2 shows the quality of reviews. The SR by JSAG Schouten[12] which was

Table 1: Types of evidence statement and the level of evidence that was required to support each statement

Evidence statement	Level of evidence
Sufficient evidence from reviews to either support or discount the effectiveness of an intervention	Clear statement from one or more core reviews based on multiple robust studies, or consistent evidence across multiple robust studies within one or more core reviews, in the absence of a clear and consistent statement in the review(s)
Tentative evidence from reviews to either support or discount the effectiveness of an intervention	A tentative statement from one or more core reviews based on consistent evidence from a small number of robust studies or multiple weaker studies, or consistent evidence from a small number of robust studies or multiple weaker studies within one or more reviews, in the absence of a clear and consistent statement in the review(s), or conflicting evidence from one or more core reviews, with the strongest evidence weighted towards one side (either supporting or discounting effectiveness) and a plausible reason for the conflict, or consistent evidence from multiple robust studies within one or more supplementary reviews, in the absence of a core review
Insufficient evidence from reviews to either support or discount the effectiveness of an intervention	A statement of insufficient evidence from a core review, or Insufficient evidence to either support or discount the effectiveness of an intervention (either because there is too little evidence or the evidence is too weak), in the absence of a clear and consistent statement of evidence from (a) core review(s), or Anything less than consistent evidence from multiple robust studies within one or more supplementary reviews no core or supplementary reviews of the topic identified, due possibly to a lack of primary studies

Adapted from Ellis *et al.* 2003,[11] Norah Palmateer *et al.* 2009[18]

Table 2: JBI critical appraisal quality score and summary of conclusions of the retrieved reviews

First author, year published (reference)	JBI quality score	Authors' conclusion
"Systematic" in title, abstract or methods		
Regis Bruni Andriolo, 2006[14]	0.7	Evidence demonstrates that bevacizumab alone or combined with PDT, focal photocoagulation and triamcinolone is more effective for neovascular diseases
Jamie M Pitlick, 2012[16]	0.5	Bevacizumab appears to be effective for AMD when compared to verteporfin PDT or pegaptanib
Jan S.A.G Schouten, 2008[12]	0.9	Visual acuity improves and central retinal thickness decreases in patients with exudative AMD after bevacizumab
Focke Ziemssen, 2009[13]	0.8	Bevacizumab appears to be safe and effective for AMD in the short term
S Jyothi, 2010[19]	0.7	There is sufficient evidence to advocate the effective use of OCT-guided administration of intravitreal bevacizumab for neovascular AMD
Other reviews with language that implied a critical and comprehensive intent		
Christine Schmucker, 2012[20]¶	0.9	Evidence from head-to-head raised concern about increased risk of ocular and systemic adverse events with bevacizumab
Christine Schmucker, 2010[21]¶	1	The studies of bevacizumab show too many methodological limitations to rule out major safety concerns
Shalini S Lynch, 2007[22]†	0.3	Uncontrolled studies support the benefit of IVB in neovascular AMD, in the short term
Paul Mitchell, 2011[2]†	0.4	In contrast to ranibizumab, current safety data for bevacizumab are incomplete and not yet robust
Derrick P Smit, 2007[23]†	0.3	Evidence suggests that intravitreal bevacizumab alone or in combination has beneficial effect in various neovascular and edematous retinal conditions

¶These reviews were not included as they did not fulfill the review's inclusion criteria. These studies primarily looked at the safety of bevacizumab, without focusing on its effectiveness. †Major criteria for quality appraisal were not satisfactorily fulfilled, hence not included. JBI: Joanna briggs institute

of good quality [Table 2] showed improvements in visual acuity and decrease in central retinal thickness in patients with exudate AMD after bevacizumab [Table 3]. RCT's showed that intravitreal bevacizumab was more effective than PDT with a mean change in visual acuity (VA) of +12.8 ETDRS letters (range +11 to +14) and weighted mean change for CRT of 129μm (range 100 to 202). The before-after studies of bevacizumab showed a mean change in VA of +8.6 letters (range +2 to +26) and change in CRT was 90 um (range 46 to 190). Review by Ziemssen *et al*.,[13] found off-label use of bevacizumab superior to PDT, in the short term, however the evidence was of moderate quality (2b level of evidence) primarily from before-after studies, case series and RCT's of bevacizumab for neovascular AMD. Andriolo *et al*.,[14] in their meta-analysis showed that BCVA was higher among those treated with bevacizumab than those in the PDT group (risk ratio, RR, 0.49; 95% confidence interval (CI), 0.31 to 0.78; $P = 0.01$). Jyothi *et al*., summarized the findings from 5 RCT's and 50 observations studies that met "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) criteria.[15] The review showed Intravitreal bevacizumab led to mean gain in vision at 3 months (+7.76 ± 5.4 ETDRS letters (range +2 to +14.4); this effect was maintained at 6 months in studies with longer follow-up. Review by Pitlick *et al*.,[16] summarized

Table 3: Quality score of JBI critical appraisal checklist by 2 independent reviewers

Reviewer	Quality score, mean (95% CI)
Reviewer 1*	7.2 (6.5-7.9)
Reviewer 2*	6.8 (6.1-7.5)
Pooled score	7 (6.8-7.2)
Adjudicated score	7 (6.2-7.8)

*These scores are before adjudication. CI: Confidence interval, JBI: Joanna briggs institute

Table 4: Validity assessments with JBI critical appraisal check list after adjudication

Index	No (%)	Yes (%)
Is the review question clearly and explicitly stated?	0	5 (100)
Was the search strategy appropriate?	3 (60)	2 (40)
Were the sources of studies appropriate?	2 (40)	3 (60)
Were the inclusion criteria appropriate for the review question?	2 (40)	3 (60)
Were the criteria for appraising studies appropriate?	1 (20)	4 (80)
Was critical appraisal conducted by two or more reviewers independently?	1 (20)	4 (80)
Were there methods used to minimize error in data extraction?	4 (80)	1 (20)
Were the methods used to combine studies appropriate?	1 (20)	4 (80)
Were the recommendations supported by the reported data?	1 (20)	4 (80)
Were the specific directives for new research appropriate?	2 (40)	3 (60)

JBI: Joanna briggs institute

findings from 4 RCT's, the review showed that bevacizumab in comparison to verteporfin PDT or pegaptanib to be superior in improving VA and reversing vision loss. Bevacizumab when compared to ranibizumab was found to have equivalent efficacy and significantly less expensive.

Discussion

Systematic reviews in ophthalmology are increasing at a rapid pace, but little information is available on the quality of these reviews. This systematic review of reviews appraises the quality of evidence from SRs on effectiveness of bevacizumab for neovascular AMD. Overall, the published reviews on this topic were of good quality, the reviews used 7 of 10 best practices for an objective and systematic methodology as enumerated by the JBI quality appraisal checklist with an *a priori* study design.

Bias arising from publication has an important influence on the results of systematic reviews and is more difficult to detect and adjust for than other forms of bias. Thus, when searching for studies to include in a systematic review, it is critical that the literature search strategy is explicitly described, comprehensive, and inclusive of both unpublished and published research.[19] The description of the search strategy provides some assurance that the authors have conducted a comprehensive, detailed, and an exhaustive search for literature relevant to the study question. The search strategy and sources of studies were found to be appropriate for 40% and 60% of the reviews respectively. Another key feature of the systematic review is to assess bias, to assess the funding sources and financial conflicts of authors as they can influence the outcomes the studies. Industry funded studies are more likely to have results that favor their product, even when controlling for other methodological biases. In our review, only one study had disclosed the conflict of interest,[2] this study also had much methodological weakness and hence was not included.

A well-conducted systematic review provides readers with an accurate summary and defensible synthesis of the available evidence. The inclusion of a methods section is essential for the transparency of results and provides the reader with the means to reproduce the review if need be. In the absence of these basic methodological features, conclusions shown in reviews may be little more than personal subjective opinions informed by the scientific evidence but not based on strong methodological grounds.[17] In this review of the reviews we found that none of the reviews were rated as a 10 out of 10 for quality, moreover 1 review had significant flaws, the methods sections of this review was insufficient and therefore difficult to evaluate. As far as the quality of the systematic review is concerned there is scope for improvement. We recommend that ophthalmology journals should adopt uniform reporting standards for systematic reviews; this would pave way for high-quality systematic reviews in ophthalmology literature.

The review points to the overwhelming evidence available in support of bevacizumab for AMD, intravitreal bevacizumab was associated with a mean gain in visual acuity of 7.76-12.8 ETDRS letters and mean decrease in CRT of 129μm after intravitreal bevacizumab. We do not have other systematic reviews of bevacizumab for neovascular age related macular degeneration with which to compare our conclusions, but they are consistent with the conclusions of 7 of the 9 most recent systematic reviews.

Limitations

Our study is a review of systematic reviews. There are some inherent weaknesses in this approach. In general due to resource constraints, we relied on the information in the included reviews. The quality of the reviews may vary; the reviews may have done a poor job in specifying their inclusion and exclusion criteria, the searches may not be comprehensive, the review authors may not have assessed or extracted data from the primary studies adequately, nor analyzed and synthesized the findings across the studies properly. But even using high quality reviews, we necessarily lose information and details that we can only find if we go back to the primary studies. Our literature search only covered the three databases and hand searching was not done due to resource constraints. Not withstanding the previously mentioned concerns, to our knowledge, this is the first study which appraises the quality of published systematic reviews on bevacizumab for neovascular AMD.

Conclusion

Reviews have found bevacizumab to be effective for neovascular AMD when used either alone or in combination with alternates

Table 5: Selected reviews published on intravitreal bevacizumab and age-related macular degeneration by outcome and year published

First author, year published	Databases searched	Types of studies: Inclusion and exclusion	No of studies reviewed	RCT's┤	Methods used to synthesize study results
Jan SAG Schouten, 2009[12]	Medline, Embase, the Cochrane Controlled Trials Register and references from included articles, March 2008	Randomised controlled trials, nonrandomised controlled studies, or before-and-after studies in more than one patient. Studies with systemic or intravitreal therapy were included. Studies were excluded that did not have VA as the primary outcome, had as the primary objective to study differences between subgroups, or included also patients other than patients with exudative AMD	26	3	Data tabulated and presented with a table of narrative findings
Regis Bruni Andriolo, 2009[14]	Medline (1966 to June 2008), Controlled Trials Register of the Cochrane Collaboration (2008, issue 2) and Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) (1982 to June 2008) and reference lists	Randomized or quasi-randomized clinical trials that tested bevacizumab alone or in association with other alternates. The condition of interest was a diagnosis of ocular diseases and conditions including AMD, coreneal neovascularization, retinal aniomatous proliferation or angiogenic retinal diseases. Studies in which the analysis unit was eyes were not included	9	9	Data tabulated and Meta-analysis done
Focke Ziemssen, 2009[13]	Medline, 1 June 2005 and 31 July 2008	Patients with subfoveal CNV secondary to neovascular AMD were included, studies reporting interventions with bevacizumab monotherapy and reporting visual acuity as a primary outcome measure were included. Congress reports and non-English language studies were excluded	33	4	Narrative summary with tabulation of the results of included studies
Jamie M Pitlick, 2012[16]	MEDLINE (1976-September 2011) and EMBASE (1973-September 2011)	All randomized clinical trials published in English with data assessing the safety and efficacy of bevacizumab for nARMD	4	4	Narrative summary of the results of included studies
S Jyothi, 2010[19]	MEDLINE (2005 to January 2009) and the National Institutes of Health clinical trial databases (up to January 2009)	Randomized controlled trials and observational case series with at least 3-month follow-up, both prospective and retrospective, which met the Strengthening the Reporting of Observational Studies in Epidemiology criteria	55	5	Data tabulated and presented with a table of narrative findings of the included studies

┤Randomized clinical trials. AMD: Age-related macular degeneration, CNV: Choroidal neovascularization, RCTs: Randomized controlled trials, STROBE: Strengthening the reporting of observational studies in epidemiology

such as PDT or Pegatanib. This study also highlights the quality of systematic reviews examining the effectiveness of bevacizumab for neovascular age related macular degeneration, highlighting the methodological shortcomings and the need for uniform reporting of the preferred items for systematic reviews in ophthalmology literature.

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Appendix I

Study eligibility checklist

Author and year_____

Journal_____

Title_____

Does the study fulfill the inclusion criteria?

A. Study design - Systematic Review?

□ YES

□ NO

B. Are there explicit statements of search methods, inclusion, exclusion criteria and data synthesis?

□ YES

□ NO

C. Participants - patients with neovascular AMD

□ YES

□ NO

D. Intervention - systemic/intravitreal bevacizumab

□ YES

□ NO

E. Outcome - Does the study evaluate the effect of the intervention on:

□ Best Corrected Visual Acuity

□ Central retinal thickness

Appendix II

Data extraction form

Appendix II: Data extraction form

Year	Author	No: of studies	Inclusion criteria	Exclusion criteria	Participants	Interventions	Outcomes	Data pooled/ not pooled	Effect estimates

Appendix III

JBI critical appraisal checklist for systematic review

1. Is the review question clearly and explicitly states?
2. Was the search strategy appropriate?
3. Were the sources of studies adequate?
4. Were the inclusion criteria appropriate for the review question?
5. Were the criteria for appraising studies appropriate?
6. Was critical appraisal conducted by two or more reviewers independently?
7. Were the methods used to minimize error in data extraction?
8. Were the methods used to combine studies appropriate?
9. Were the recommendations supported by the reported data?
10. Were the specific directives for new research appropriate?

Appendix III: JBI critical appraisal checklist for systematic review

Reviewer:	Date:
Author:	Year:
Record number:	

Overall appraisal:	Include	Exclude	Seek further information
Comments, reason for including or excluding:			