Preoperative intravitreal bevacizumab for proliferative diabetic retinopathy patients undergoing vitrectomy- First update

Efraín Pérez-Argandoña[a,b], Juan Verdaguer[a], Sergio Zacharías[a], Raúl González[b,c *]

[a] Fundación Oftalmológica Los Andes, Santiago, Chile
[b] Proyecto Epistemonikos, Santiago, Chile
[c] Departamento de Oftalmología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

***Corresponding author** raulgonzalezc@gmail.com

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Key words proliferative diabetic retinopathy, bevacizumab, vitrectomy, Epistemonikos, GRADE.

Abstract

Update

This Living FRISBEE (Living FRIendly Summary of the Body of Evidence using Epistemonikos) is an update of the summary published in December 2014.

Introduction

Proliferative diabetic retinopathy can cause severe vision loss and even blindness if left untreated. Vitrectomy is often required in the treatment of more severe cases. Preoperative administration of bevacizumab, a humanized anti-vascular endothelial growth factor would improve intraoperative variables that facilitate surgery and improve postoperative course.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified five systematic reviews including 16 studies overall, of which 14 were randomized trials. We concluded the preoperative use of intravitreal bevacizumab reduces the rate of vitreous hemorrhage in the early postoperative period, and probably also in the late postoperative period, but its effect on visual acuity is not clear. Furthermore, it probably decreases the surgical time and may decrease the incidence of iatrogenic retinal breaks. Although we are uncertain whether preoperative bevacizumab decreases intraoperative bleeding, it may reduce the need for endodiathermy.

About this update

This Living FRISBEE (Living Friendly Summary of the Body of Evidence using Epistemonikos) is an update of the summary published in December 2014 (doi: 10.5867/medwave. 2015.6160)[1], based on a new systematic review[2] and the update[3] of one of the reviews already included in the previous version[4]. These systematic reviews included four new trials[5-8] compared to the previous version of this summary.

Considering the new evidence, we have redefined the relevant outcomes, updating and conducting new analyses with the available data. The evidence incorporated in this summary leads to changes related to the certainty of the evidence on the outcomes associated with intraoperative variables, the addition of postoperative outcomes and the reformulation of the adverse effects analysis previously published.

Problem

Proliferative diabetic retinopathy, neovascularization and fibrous proliferation lead to blindness if not treated appropriately. Patients with this condition may have complications such as vitreous hemorrhage, tractional retinal detachment or extensive fibrovascular proliferation requiring vitrectomy as part of their treatment. This procedure has the risk of intraoperative bleeding, which decreases the visibility during the surgery, with the subsequent risk of complications during the postoperative period.

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor. Its antiangiogenic properties would be useful in patients with active neovascularization who undergo vitrectomy, facilitating surgery by decreasing intraoperative complications such as bleeding and decreasing the occurrence of vitreous hemorrhage during the postoperative period.

Key messages

- Preoperative intravitreal injection of bevacizumab reduces the incidence of vitreous hemorrhage in the early postoperative period and probably do so in the late postoperative period.
- We are uncertain whether the use of bevacizumab prior to vitrectomy leads to better visual acuity as the certainty of the evidence has been assessed as very low.
- Preoperative use of bevacizumab probably reduces total surgical time.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found five systematic reviews[2,3,9-11] including 16 primary studies[5-8,12-23], of which 14 are randomized trials[4-7,12,13,15-17,19-23]. This table and the summary in general are based on the latter, since the observational studies did not increase the certainty of the existing evidence, nor did they provide relevant additional information.
What types of patients were included*	Most trials included patients without distinction by sex or age. Only one trial excluded patients under 18 years of age[4]. The age reported by the different trials ranged from 44[12] to 62 years[5]. All trials included patients with indication of pars plana vitrectomy for complications of proliferative diabetic retinopathy, mainly vitreous hemorrhage [5,7,8,12,13,15,19,21-23] and tractional retinal detachment[5,7,8,12,13,15-23]. Only one trial excluded patients with vitreous hemorrhage of any grade[16], while another trial excluded cases of dense vitreous hemorrhage preventing preoperative grading of fi-

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

	brovascular membranes[5]. One trial did not consider cases of tractional-rhegmatogenous retinal detachment[19] and one trial excluded retinal detachment with macular involvement[20]. There was great variability in the exclusion criteria reported. It should be noted that most trials excluded patients with previous intraocular surgery, especially vitreoretinal surgery[5,6,8,13,16,17,21,22]; five trials excluded patients with history of myocardial infarction, stroke or thrombotic events[4,7,13,16,22]; four trials excluded patients with blood coagulopathy, alterations in coagulation tests or use of antithrombotics other than aspirin[13,16,21,22]. Only two trials excluded pregnant women[5,15] and two excluded previous intravitreal injection of bevacizumab[15,17]. The trials included 674 eyes in 649 patients, all of them adults. Four trials included more than one eye per patient[5,8,19,21].
What types of interventions were included*	All trials compared intravitreal injection of bevacizumab before vitrectomy against vitrectomy alone. Only three trials used simulated injection in the control group[5,15,19]. Intravitreal bevacizumab was used in the intervention group in different administration protocols. The dose was mostly 1.25 mg in 0.05 ml[5-7,12,13,15,19-23]. Two trials used higher doses of bevacizumab in the same concentration: one of them used 2.5 mg[17] and another 1.5 mg[16]. The concentration of bevacizumab was the same in all trials except in the most recent one that used a significantly lower concentration with a dose of 0.16 mg in 0.05 ml[8]. The timing of the intervention ranged from 1 to 20 days before surgery. Most trials administered bevacizumab at least 7 days prior to vitrectomy[5,6,7,8,12,13,15,17,20,22]. One trial administered bevacizumab 14 days before the procedure[16]. In two trials patients were randomized to one of three groups: control and two intervention groups, which varied in the preoperative time intervals[19,21]: 7 or 20 days before vitrectomy respectively[19] and 1 to 14 days prior vitrectomy, with an average of 4.9 days[21]. Data obtained from the 37 eyes of this study[21] receiving intraoperative bevacizumab were excluded when meta-analyses were performed.
What types of outcomes were measured	There is great variability in the outcomes measured by the trials. These can be classified into intraoperative variables, postoperative course and adverse effects: • Intraoperative variables: total surgical time, intraoperative bleeding, use of endodiathermy (cauterization of retinal blood vessels), iatrogenic retinal tears and use of tampons such as silicone, oil, gas, perfluorocarbon. • Postoperative outcomes: Best corrected visual acuity, early (< 4 weeks) or late (> 4 weeks) postoperative vitreous

	hemorrhage, resorption time of vitreous hemorrhage, attachment of the retina. • Injection-related and surgery-related adverse events: systemic adverse events and systemic thrombosis, mainly myocardial infarction or stroke, local adverse effects such as endophthalmitis, retinal detachment, increased intraocular pressure, new cases of rubeosis, neovascular glaucoma, cataract progression, corneal erosions, anterior chamber reaction, uveitis, among others.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of Findings

The information about the effects of bevacizumab is based on 13 randomized trials including 674 eyes in 649 patients[5-8,12,13,15-17,19-22]. One of the trials[23] did not provide information about any outcome of interest.

Nine trials reported early postoperative vitreous hemorrhage (475 eyes)[6-8,12,15,17,20-22] and six reported late postoperative vitreous hemorrhage (269 eyes)[7,12,17,20-22]. Six trials reported visual acuity during postoperative follow-up (270 eyes)[5,12,17,19-21], six assessed total surgical time (246 eyes)[8,12,13,17,19,20], six intraoperative bleeding (218 eyes)[5,12,13,15,19,20], six intraoperative use of endodiathermy (276 eyes)[6,8,12,17,20,22] and seven reported iatrogenic retinal tears (333 eyes)[8,12,13,15,19,20,22].

Eight trials assessed systemic adverse events including myocardial infarction, stroke or systemic thrombosis (366 eyes)[5,8,12,13,15,16,19,21] and six endophthalmitis (318 eyes)[8,13,15,16,19,21].

The summary of findings is as follows:

Postoperative course:

- Preoperative use of bevacizumab reduces the incidence of early postoperative vitreous hemorrhage (< 4 weeks) (high certainty evidence).
- Preoperative use of bevacizumab probably reduces the incidence of vitreous hemorrhage in the late postoperative period (> 4 weeks) (moderate certainty evidence).
- We are uncertain whether the use of bevacizumab prior to vitrectomy leads to a change in visual acuity in postoperative follow up equal to or greater than 3 months, as the certainty of the evidence has been assessed as very low.

Intraoperative Variables:

- Preoperative use of intravitreal bevacizumab probably reduces total surgical time (moderate certainty evidence).
- We are uncertain whether the use of preoperative bevacizumab reduces the occurrence of intraoperative bleeding as the certainty of the evidence has been assessed as very low.
- The use of preoperative bevacizumab may reduce the need for use of endodiathermy and the occurrence of iatrogenic retinal tears (low certainty evidence).

Adverse effects:

- We are uncertain whether the use of bevacizumab increases the risk of systemic adverse events such as myocardial infarction, stroke or systemic thrombosis as the certainty of the evidence has been assessed as very low.
- We are uncertain whether the use of intravitreal bevacizumab is associated with a higher rate of local adverse events as the certainty of the evidence has been assessed as very low.

Intravitreal injection of bevacizumab prior to vitrectomy for proliferative diabetic retinopathy				
Patients	Proliferative diabetic retinopathy requiring vitrectomy			
Intervention	Intravitreal bevacizumab prior to vitrectomy			
Comparison	Vitrectomy alone, without preoperative bevacizumab, with or without preoperative sham injection.			
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT Bevacizumab	WITH Bevacizumab		
	Difference: eyes per 1000			
Early postoperative vitreous hemorrhage (<4 weeks)	311 per 1000	88 per 1000	RR 0.35 (0.24 to 0.57)	⊕⊕⊕⊕ High
	Difference: 223 eyes less (Margin of error: 133 to 242 less)			
Late postoperative vitreous hemorrhage (<4 weeks)	209 per 1000	104 per 1000	RR 0.56 (0.31 to 1.0)	⊕⊕⊕◯[1] Moderate
	Difference: 105 eyes less (Margin of error: 0 to 144 less)			
Best corrected visual acuity	1.2 LogMAR**	0.82 LogMAR	--	⊕◯◯◯[1,2,3] Very low
	MD: 0.38 less LogMAR (Margin of error: 0 to 0.77 LogMAR less)			
Total surgical time	81 minutes	57 minutes	--	⊕⊕⊕◯[2] Moderate
	MD: 24 minutes less (Margin of error: 15 to 32 less)			
Intraoperative bleeding	918 per 1000	541 per 1000	RR 0.59 (0.34 a 1.04)	⊕◯◯◯[1,2,3] Very low
	Difference: 377 eyes less (Margin of error: 606 less to 37 more)			
Intraoperative use of endodiathermy	4 applications	1.5 applications	--	⊕⊕◯◯[2,3] Low
	MD: 2.5 applications less (Margin of error: 1 to 4 less)			
Iatrogenic retinal tears	208 per 1000	114 per 1000	RR 0.55 (0.31 a 0.99)	⊕⊕◯◯[1,2] Low
	Difference: 94 eyes less (Margin of error: 0 to 146 less)			
Systemic adverse events	There were no systemic adverse events such as myocardial infarction, stroke or systemic thrombosis in any treatment arms of the randomized trials.			⊕◯◯◯[2,4,5] Very low
Local adverse events	Local adverse events occurred with low frequency and there was no difference between treatment arms. In particular, no case of endophthalmitis was reported in any of the treatment arms.			⊕◯◯◯[2,4,5] Very low

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).
*The risk WITHOUT bevacizumab is based on the risk in the control group of the trials. The risk WITH bevacizumab (and its margin of error) is calculated from relative effect (and its margin of error).
** Logarithm of the minimum angle of resolution.
[1] The certainty of the evidence was downgraded in one level for imprecision because the confidence interval includes the possibility of no effect.
[2] The certainty of the evidence was downgraded in one level due to risk of bias. Only four trials reported a double-blind study design [4], [7], [15], [19] and two reported that only the surgeon was blinded to the intervention [17], [22].
[3] The certainty of the evidence was downgraded for inconsistency (I2 of 82% for best corrected visual acuity outcome; I^2 of 97% for intraoperative bleeding; I^2 of 96% for the intraoperative use of endodiathermy).
[4] The certainty of the evidence was downgraded in one additional level due to risk of bias because it is not possible to rule out selective adverse effect reporting.
[5] The certainty of the evidence was downgraded in two levels due to indirectness of the evidence. The included studies were not designed to research low-frequency adverse events, the interventions were variable (only two of the six studies reporting endophthalmitis used sham injection; dose of bevacizumab and the time interval of the intervention was variable) and the follow-up time was variable.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

This evidence applies to adults with indication of vitrectomy for complications of proliferative diabetic retinopathy, particularly vitreous hemorrhage and tractional retinal detachment.

Patients with previous intraocular surgeries other than cataract surgery, especially vitreoretinal surgeries, were excluded.

This evidence does not apply to patients with history of major cardiovascular events such as myocardial infarction, stroke or systemic thrombosis, and patients with coagulopathy, abnormal coagulation tests and/or use of anticoagulants.

Pregnant women were also excluded.

About the outcomes included in this summary

The outcomes included in this summary are consistent with those considered critical for decision-making by most trials, systematic reviews and the main clinical guidelines.

The evidence on how patients value different outcomes in diabetic retinopathy shows that visual acuity is the most important[24,25]. Unfortunately, the effect of using bevacizumab prior to vitrectomy on this outcome is still unclear.

Balance between benefits and risks, and certainty of the evidence

It is not possible to estimate risk/benefit balance properly since there is uncertainty with respect to visual acuity. However, there is evidence that shows benefits in postoperative vitreous hemorrhage and the most important surgical variables.

None of the trials reported cases of systemic adverse events for either of the two treatment arms. However, the follow-up carried out by the trials was limited; 6 months in most trials, but in some cases as short as one month[8,15].

The systemic application of bevacizumab in patients with colorectal cancer has been associated with higher treatment-related mortality, serious cardiovascular adverse effects, hypertension and arterial thrombotic events[26]. Considering plasmatic presence of the drug has been described after intravitreal administration[27], it is reasonable to take caution when considering the evidence presented.

However, this risk has not been demonstrated in the intravitreal application of bevacizumab. Systematic reviews that assessed the safety of this intervention in different ophthalmological conditions have not shown an increased risk of serious adverse effects, such as major cardiovascular events, but more evidence is needed to carry out an adequate evaluation[28-31]. A recent publication by the Canadian Agency for Drugs and Technology in Health, concludes that it is still not clear whether the risk of thromboembolic events is significantly higher in a population using intravitreal anti-VEGF compared to a similar population (that has a high basal risk) that does not use this treatment, and that the risk would not be greater in one type of anti-VEGF compared to another[32].

Therefore, with the intravitreal application of bevacizumab, the cardiovascular and systemic risks evidenced with its systemic application have not been reported so far. However, the current evidence is insufficient to obtain definitive conclusions.

Regarding to local adverse events, these occurred with low frequency in the included trials (mainly cases of early transient elevation of intraocular pressure) and there was no difference between the intervention and control groups. No cases of endophthalmitis were reported in the six trials that reported it. However, this is probably due to the small sample size. It is known that the risk of endophthalmitis is very low, but it exists[32]. A recent meta-analysis, which analyzed 503,890 intravitreal injections of various anti-VEGF, reports an average incidence of 0.039% for bevacizumab, with no significant differences when compared with ranibizumab or aflibercept[33]. This is a point to bear in mind, but it should also be noted that the included patients with severe ophthalmological conditions requiring vitrectomy that have a high-risk of complications such as endophthalmitis, which occurs on average in 0.05% of cases[34].

Resource considerations

Because the use of bevacizumab prior to a vitrectomy has been recently proposed and its clinical effects are still under investigation, no studies assessing the cost-effectiveness of this intervention have been conducted.

The positive effect of bevacizumab on intraoperative variables such as total surgical time could contribute to lower costs and make the intervention more efficient. The favorable effect on clinical outcomes could contribute to improve the quality of life. However, its effect on visual acuity is still unclear.

Since bevacizumab is currently a high-cost drug, its use prior to a vitrectomy should be assessed in detail in contexts where there are major resource constraints.

What would patients and their doctors think about this intervention

Due to the great importance that patients attribute to visual acuity, in scenarios without major resource constraints, some patients may be inclined to use a therapy with a potential benefit in this outcome, although the certainty of the evidence is very low.

Physicians may be inclined to use this option for its favorable effects on intraoperative variables such as total surgical time in addition to the decrease in the incidence of postoperative vitreous hemorrhage.

Differences between this summary and other sources

In general terms, our conclusions are concordant with the included systematic reviews identified regarding the outcomes of early postoperative vitreous hemorrhage, visual acuity, total surgical time, use of endodiathermy, iatrogenic retinal tears and adverse effects.

With regard to late postoperative vitreous hemorrhage, there are differences in the results obtained by our review and three of the systematic reviews[2,3,10]. These are mainly explained by differences in the primary studies included. Our meta-analysis is the only one that considers all randomized trials with information available on this outcome. However, the certainty of the evidence is moderate so it could change with future trials.

It is expected that the effect of preoperative bevacizumab on the incidence of vitreous hemorrhage in the late postoperative period (> 4 weeks) is less than in the early postoperative period (< 4 weeks) or even null, as the half-life of the drug is short. Pharmacokinetic studies, both in animal models and humans, have shown the half-life of bevacizumab in the vitreous humour would be approximately 4 to 5 days[35-37], and would be minimally detectable up to 30 days. However, it could be detected in the retina for up to 14 days [18], and there could be effects that persist independent of the presence of the drug. New formulations of bevacizumab are being studied, such as sustained-release models, that could eventually increase the effect of the drug on the late postoperative period[37]. The half-life would be modified with the dose administered[38], so the most effective dose would have to be assessed. Furthermore, the half-life of the drug in vitrectomized eyes would be considerably lower[36] and the clinical effect might also be less in previously vitrectomized eyes, cases that were excluded by most of the randomized trials. All these pharmacokinetic aspects should be investigated in advance with adequate clinical studies that provide sufficient evidence to formally assess if they might have real clinical implications or not.

With regard to the occurrence of intraoperative bleeding, there are subtle differences in relation to the results and interpretation of the evidence, which are due mainly to the primary studies included and the statistical analysis model used for comparison (in our case we use relative risk). Similar to the other three systematic reviews[2,9,10], our results show that there is no certainty whether preoperative bevacizumab decreases the occurrence of intraoperative bleeding because the certainty of the evidence is very low. In three[5,12,20] of the six trials reporting data for this outcome, intraoperative bleeding occurred in almost all patients in both treatment groups. A probable interpretation is that the effect of bevacizumab decreases the severity of intraoperative bleeding rather than the occurrence of it, which would be difficult to avoid given the context of neovascularization presented by these patients. In this sense, the frequency of use of endodiathermy was considered by several trials as an indicator of bleeding severity, and the evidence shows with more certainty that the use of preoperative bevacizumab would decrease the number of intraoperative applications of endodiathermy.

The key messages of our summary are concordant with the main guidelines identified, which suggest bevacizumab should be considered preoperatively in eyes with proliferative diabetic retinopathy undergoing vitrectomy[39,40]. Likewise, it is not opposed to other guidelines that indicate that this therapeutic application is still in investigation[41], since the certainty of the available evidence is not the optimal regarding several outcomes.

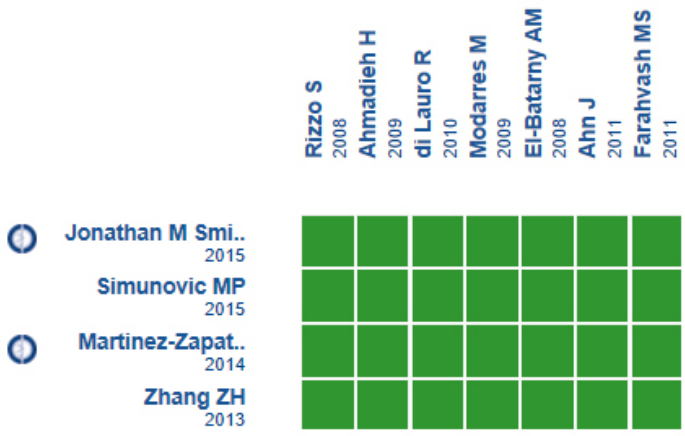
Could this evidence change in the future?

It is probable that the conclusions associated with the effect of the preoperative use of bevacizumab in eyes with proliferative diabetic retinopathy undergoing vitrectomy will change in the future, particularly in relation to their effect on the visual acuity.

Three randomized trials responding this question were identified in the International Clinical Trials Registry Platform of the World Health Organization, but they had planned to complete the recruitment more than 5 years ago and still do not report results[42,43,44].

We did not identify ongoing systematic reviews in PROSPERO (International prospective register of systematic reviews) assessing this question. How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Preoperative bevacizumab for proliferative diabetic retinopathy.

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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Correspondence to
Centro Evidencia UC
Pontificia Universidad Católica de Chile
Diagonal Paraguay 476
Santiago
Chile