A Systematic Analysis of the Off-Label Use of Bevacizumab for Severe Retinopathy of Prematurity

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• PURPOSE: **To examine the quality of evidence and the variability in the off-label use of bevacizumab (Avastin; Genentech Inc, South San Francisco, California, USA) in the treatment of retinopathy of prematurity (ROP) and to discuss the implications for the design of future randomized controlled trials.**

• DESIGN: **Systematic literature review.**

• METHODS: **A systematic review of the literature indexed by Ovid MEDLINE, EMBASE, and the Cochrane database was performed with a broad and inclusive search strategy. All case reports and retrospective and prospective trials in peer-reviewed journals reporting the use of bevacizumab in ROP were included.**

• RESULTS: **Nine articles, including 6 case reports, 2 retrospective studies, and 1 prospective case series representing 77 eyes of 48 infants, were selected for the review. The doses used ranged from 0.4 to 1.25 mg, with 0.75 mg being the most common, used in 3 of the 9 studies. A total of 8 of the 11 eyes in the case received bevacizumab as a first-line therapy and two articles noted worsening of an already present retinal detachment. One retrospective study and the prospective case series used bevacizumab alone, whereas the other retrospective study used bevacizumab before and with retinal surgery.**

• CONCLUSIONS: **Considerable variability exists in how bevacizumab is used for the treatment of ROP in the literature to date. Further randomized control trials are warranted and should aim to assess statistically the optimal timing, frequency, and dose of the drug. Careful attention should be given to the potential for systemic complications and long-term effects of intravitreal bevacizumab in infants. (Am J Ophthalmol 2009;xx:xxx. © 2009 by Elsevier Inc. All rights reserved.)**

RETINOPATHY OF PREMATURITY (ROP) IS A PROLIFERative disorder of the developing retina that continues to be a major cause of blindness of children in the developed and developing world.[1,2] It is currently understood that ROP is a biphasic disease consisting of an initial phase of oxygen-induced vascular obliteration followed by a period of hypoxia-induced vessel proliferation.[3] Vascular endothelial growth factor (VEGF) is an angiogenic cytokine that is central to the development of both pathogenic phases. In the normally developing retina, VEGF is released in response to the oxygen demand of this neural tissue, leading to further development of blood vessels from the optic nerve to the periphery.[4,5] In response to elevated oxygen compared with the relatively hypoxic intrauterine environment, however, the normal demand is suppressed. Subsequently, diminished oxygen tensions may lead to an increased wave of VEGF expression and abnormal growth of new vessels from the retina to the vitreous accompanied by fibrovascular tissue.[6]

Intravitreal injection of a neutralizing anti-VEGF molecule has been demonstrated to diminish the neovascular response significantly in animal models.[7,8] Consequently, bevacizumab (Avastin; Genentech Inc, South San Francisco, California, USA), a full anti-VEGF antibody of 149 kD approved for use in the treatment of colorectal cancer and used off-label for the treatment of exudative age-related macular degeneration (AMD)[9] and proliferative diabetic retinopathy (PDR),[10] has been used in the treatment of severe ROP without randomized controlled trials or evidence for its use. However, it is not difficult to imagine how such a therapy could offer advantages over conventional laser photocoagulation or cryotherapy in ROP treatment, especially for zone I and aggressive posterior ROP cases, which often have unfavorable outcomes.[11–14] The Cryotherapy for Retinopathy of Prematurity Cooperative Study reported a 77.8% unfavorable outcome rate using cryotherapy,[15] and the Early Treatment for Retinopathy of Prematurity Cooperative Group reported a 55.2% unfavorable outcome rate using laser photocoagulation in zone I disease.[16]

Uncertainties clearly remain with respect to the systemic effects, dosing, frequency, timing, and adjunct therapies to be used with bevacizumab. Moreover, there has been considerable variability in how this drug has been used even in the reports published to date. It was the goal of the current study systematically to review the use of bevacizumab in ROP and to synthesize the currently available clinical data to provide the best evidence to this

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TABLE 1. Search Strategy Using Ovid MEDLINE and EMBASE for Reports on the Use of Bevacizumab for Severe Retinopathy of Prematurity

	Query	Results (English)
MEDLINE (Ovid 1950 to week 4 of February 2009)		
1	"Retinopathy of prematurity" [MeSH]	2626
2	"Retinopath* of premat*" [title/abstract]	3178
3	"Retrolental fibroplasia*" [title/abstract]	561
4	"Prematurity retinopath*" [title/abstract]	2
5	1 OR 2 OR 3 OR 4	3259
6	"Angiogenesis inhibitors" [MeSH]	6638
7	"Bevacizumab" [title/abstract]	1918
8	"Avastin" [title/abstract]	398
9	6 OR 7 OR 8	7776
10	5 OR 9	33
EMBASE (Ovid 1980 to week 10 of 2009)		
11	"Retrolental fibroplasia" [MeSH]	2254
12	"Retinopath* of premat*" [title/abstract]	1980
13	"Retrolental fibroplasia*" [title/abstract]	2289
14	"Prematurity retinopath*" [title/abstract]	3
15	11 OR 12 OR 13 OR 14	2746
16	"Bevacizumab" [MeSH]	6542
17	"Angiogenesis inhibitor" [MeSH]	5626
18	"Bevacizumab" [title/abstract]	6612
19	"Avastin" [title/abstract]	2429
20	16 OR 17 OR 18 OR 19	11 249
21	15 AND 20	37
22	10 OR 21	53

MeSH = Medical Subject Headings.

issue and to discuss the implications for future controlled trials.

METHODS

OVID MEDLINE (1950 TO WEEK 4 OF FEBRUARY 2009) AND EMBASE (1980 to week 10 of 2009) were searched using the medical subject headings *retinopathy of prematurity* and *angiogenesis inhibitors* and the following free text terms: *retinopathy of prematurity*, *retrolental fibroplasia*, *prematurity retinopathy*, *bevacizumab*, and *Avastin*. The relevant keywords were linked as shown in Table 1 using the Boolean operators AND/OR, and all studies were limited to the English language. The Cochrane database search also was performed for randomized control trials, systematic reviews, and meta-analyses using the same search strategy, as indicated previously. Search results were analyzed by two independent reviewers (J.A.M. and M.S.) and were included if they reported the use of bevacizumab in a case report, retrospective or prospective case series, or randomized control trials. All animal studies, abstracts, and conference proceedings that were not published in peer-reviewed journals were excluded. The reference lists of included studies and relevant reviews were scanned to identify additional potentially relevant reports.

RESULTS

THE SEARCH STRATEGY IDENTIFIED A TOTAL OF 53 ARTIcles, as demonstrated in Table 1. No results were retrieved from the Cochrane database for randomized control trials, systematic reviews, or meta-analyses. From these results, a total of 44 articles were excluded because they were animal studies (n = 13), were review articles or editorials (n = 26), were comments on the included studies without additional case reports (n = 2), were reports on the use of bevacizumab for neovascular glaucoma (n = 2), or reported only duplicate data found in an included study (n = 1). No additional articles were found by searching the references of relevant review articles or the included studies.

A total of 9 articles representing 77 eyes of 48 infants met the inclusion or exclusion criteria and were selected for the systematic review. Of these 9 articles, 6 were case reports on the use of bevacizumab in ROP,[17–22] two retrospectively reviewed the use of bevacizumab in

TABLE 2. Characteristics of the Included Case Reports of Bevacizumab for Severe Retinopathy of Prematurity

Authors, Year[Ref No.]	No. of Patients (Eyes Treated with Bevacizumab)	Gestational Age (wks)	Birth Weight (g)	State before Use of Bevacizumab (as described)	Previous Therapy for Bevacizumab-Treated Eye(s)?	Treatment Used in Conjunction with Bevacizumab	Dose of Bevacizumab Used (mg)	Favorable Outcome with Bevacizumab?
Chung and associates, 2007[18]	1 (2)	25	884	Zone I, stage 3+	No	Laser photocoagulation	0.75	Yes
Honda and associates, 2008[19]	1 (1)	23	598	Zone I, stage 4A+	Yes	None	Right eye, 0.4	No
Kong and associates, 2008[20]	1 (2)	22	350	Zone I, stage 2+	No	None	0.5	Yes
				Zone II, stage 3+	No	None	0.5	Yes
Shah and associates, 2007[21]	1 (1)	31	1170	Anterior NV after laser for AP-ROP	Yes	None	Left eye, 0.75	Yes
Lalwani and associates, 2008[22]	3 (5)	23	600	Threshold ROP	No	None	1.25	Yes
				Reactivation of NV	Yes	Laser 1 week prior	Right eye, 0.63	Yes
		24	760	Zone 1, plus disease	No	Laser photocoagulation	Right eye, 0.63	Yes
		25	835	Bilateral RD	Yes	None	Left eye, 0.63	NS
				Persistent exudation	Yes	Laser photocoagulation	Right eye, 0.63	No
				Vascular engorgement	No	None	Left eye, 0.63	Yes
Travassos and associates, 2007[17]	3 (3)	25	510	Anterior segment involvement in posterior zone II; prethreshold	No	None	Right eye, 0.75	Yes
		25	650	Anterior segment involvement in posterior zone II; prethreshold	No	None	Right eye, 0.75	Yes
		23	649	Anterior NV after laser for zone I; prethreshold	Yes	Non	Left eye, 0.75	Yes

AP-ROP = aggressive posterior retinopathy of prematurity; NS = not stated; NV = neovascularization; RD = retinal detachment.
Favorable outcome was defined as regression of the disease as described in each report, and a RD or worsening of the condition was categorized as unfavorable.

TABLE 3. Included Information in the Analyzed Case Reports of Bevacizumab for Severe Retinopathy of Prematurity

Authors, Year[Ref No.]	Zone	Stage	Extent	Pre-Bevacizumab Image	Post-Bevacizumab Image	Consent for Use Described
Chung and associates, 2007[18]	Yes	Yes	No	Yes	Yes	Yes
Honda and associates, 2008[19]	Yes	Yes	No	Yes	Yes	Yes
Kong and associates, 2008[20]	Yes	Yes	No	No	Histologic	No
Shah and associates, 2007[21]	No	No	No	No	No	No
Lalwani and associates, 2008[22]	1 of 3	No	No	Yes	Yes	Yes
Travassos and associates, 2007[17]	Yes	No	No	2 of 3	2 of 3	Yes

ROP,[23,24] and one reported a prospective study on the issue.[25] There were no randomized control trials published on the topic. The features of the included case reports are demonstrated in Table 2. There were 14 eyes of 10 patients reported in these cases, of which almost all infants had the disease in zone I or posterior zone II. Eight of the eyes received bevacizumab as a first-line therapy, and the most commonly used dose was 0.75 mg. Only one report[18] provided rationale for the use of this dose, which included no systemic or ocular complications previously reported with this amount.[17,21] Moreover, two reports[19,22] noted a worsening of an already present retinal detachment (RD), and there were two case studies that used bevacizumab immediately after laser photocoagulation.

Chung and associates and Lalwani and associates described the cases in which 0.75 and 0.63 mg bevacizumab, respectively, were used immediately after laser photocoagulation.[18,22] The former case involved the treatment of a bilateral stage 3 zone I case with severe plus disease and extensive epiretinal vascular proliferation. From postoperative day 1, a decrease in the vascular engorgement and tortuosity was noted and was well regressed with clear media when followed up 3 months later. Unlike this case, the patients presented by Lalwani and associates experienced repeated treatment with bevacizumab often supplemented with laser photocoagulation.[22] The first two cases reported in this series resulted in stabilization of the disease, unlike the third patient, who initially was referred with bilateral exudative RDs, although no additional information regarding the zone and stage of the disease were presented. After laser and bevacizumab injection on the right eye of this patient with persistent exudation, a rhegmatogenous RD resulted 3 weeks later.

The reports from Shah and associates and Travassos and associates used bevacizumab alone for the treatment of anterior neovascularization because the use of laser photocoagulation was very difficult in this situation.[17,21] All of the patients with anterior involvement in these reports experienced an unequivocally beneficial response to the intravitreal injections as defined by the extent of the neovascular regression and the complete dissolution of tunica vasculosa lentis. The first two infants treated by Travassos and associates received no prior treatment and did not require any further therapy because the neovascularization regressed and physiologic vessels developed to peripheral zone II, leaving zone III avascular.[17] The study by Shah and associates used laser, topical steroids, and cycloplegic drops before the use of bevacizumab, and, despite the regressed ROP, a bilateral lamellar cataract and iris atrophy were observed.[21] Although the condition in this report was described as aggressive posterior ROP, no further details on the condition or preoperative or postoperative images were presented. These features of the case reports are summarized in Table 3.

The treatment of stage 4A with plus disease with 0.4 mg bevacizumab subsequent to unsuccessful laser photocoagulation resulting in a further RD was described by Honda and associates.[19] Although the vascular component of the fibrovascular membrane regressed after the intravitreal injection, its appearance became fibrotic and it contracted centripetally, resulting in a funnel-like RD in the posterior retina. In the left eye, which did not receive an injection, a tractional RD also developed at 19 weeks of age, which was reattached successfully after vitrectomy. No systemic complications of the intravitreal bevacizumab injection were noted in this or any of the other case reports in the short-term.

The characteristics of the retrospective reviews and the prospective study representing 63 eyes of 38 patients are presented in Table 4. Each report was of a different design and used a different dose of bevacizumab. Kusaka and associates reported the results of a retrospective review of 14 consecutive patients with vascularly active severe ROP, all having received laser ablation therapy at a prior institution.[23] Of the 23 eyes in the study, 15 were given an initial preoperative injection of intravitreal bevacizumab, and if the disease did not resolve, vitrectomy, lensectomy or a lens-sparing vitrectomy with an intravitreal bevacizumab injection at the end of the surgery was performed 5 to 12 days later. There were 8 eyes that did not receive this initial preoperative bevacizumab because a tractional RD seemed to be approaching the macula or only mild vascular activity was present. Of the eyes that received the initial bevacizumab, 3 eyes did not receive any further treatment because of the resolution of the disease and 3 eyes experienced a progression of a tractional RD with whitening and contraction of the neovascular membranes 5 to 6 days later. These eyes that did not resolve and received the

TABLE 4. Characteristics of the Retrospective Reviews and Prospective Study of Bevacizumab for Severe Retinopathy of Prematurity

Authors, Year[Ref No]	No. of Patients	Study Type	Disease Stage at First Treatment with Bevacizumab	Dose of Bevacizumab Used (mg)	Bevacizumab Use	Outcome Measures
Kusaka and associates, 2008[23]	23 eyes of 14 patients	Retrospective case series	Zone I, 4B (9%), 4A (48%), 3 (4%); post-zone II, 4A (30%), 3 (9%)	0.5	5 to 12 days before vitrectomy and/or with vitrectomy	Final retinal attachment (100%); reduced leakage of NVM complete (9%) and partial (61%); visual acuity (mean, 0.10)
Mintz-Hittner and associates, 2008[24]	22 eyes of 11 patients	Retrospective case series	Zone I, AP-ROP (9%), 3C (18%), 3B (9%); post-zone II, 3B (64%)	0.625	Alone	Regression of ROP (100%); continued vascularization to spindle cells (100%)
Quiroz-Mercado and associates, 2008[25]	18 eyes of 13 patients	Prospective case series	Stage 4A (23%), 4B (8%); eyes unable to be graded (38%); stage 3 plus disease (69%)	1.25	Alone	Stage at 4, 12, and 38 weeks; all patients had regressed or no ROP at 38 weeks

NVM = neovascular membrane; ROP = retinopathy of prematurity.

surgery with bevacizumab all had a partially reduced fluorescein leakage of the neovascular membranes with an attached retina on follow-up with angiography. The eyes that received surgery as an initial therapy and then an intravitreal bevacizumab injection all were reported to have their retina attached at follow-up with good anatomic outcomes. Whether the lack of postoperative additional bleeding and reproliferation were a result of the postoperative bevacizumab, however, remains equivocal because of lack of controls.

The retrospective case series described by Mintz-Hittner and associates[24] evaluated the efficacy of bevacizumab alone in 22 eyes of 11 infants who did not receive any laser treatment. A 0.625-mg dose of bevacizumab was injected into all patients, 7 of whom had posterior zone II stage 3B disease, and the remaining 4 of whom had zone I aggressive posterior ROP, zone I 3C tunica vasculosa lentis, zone I 3B, and zone I 3C ROP. All eyes required only a single injection to induce regression of acute ROP and continued vascularization of the peripheral retina. Of note was the rapidly reduced engorgement of the iris and anterior tunica vasculosa lentis, which made the potential treatment with laser impossible.

Quiroz-Mercado and associates reported the results of a prospective case series in 18 eyes of 13 patients that were divided into 3 groups: group I, patients with stage 4A or 4B ROP who had no response to conventional treatment; group II, patients in which the retina could not be visualized adequately, making treatment with conventional therapies difficult; and group III, patients with high-risk prethreshold or threshold ROP.[25] All infants were treated with a 1.25-mg dose of intravitreal bevacizumab without the use of other therapies. The outcome of the treatment was evaluated at 4, 12, and 38 weeks after injection. In group I, 2 patients regressed to stage I and no disease at 4 and 12 weeks, respectively, and 2 patients required vitrectomy at 4 weeks of follow-up. In the second group of patients, 4 infants had stage I ROP and 1 was observed to have stage 3+ disease at 4 weeks, all of which regressed at 12 weeks of follow-up. The final group of patients all regressed to stage I disease at 4 weeks and no disease at 12 weeks. No ocular or systemic side effects were reported.

DISCUSSION

THE USE OF BEVACIZUMAB IN ROP HAS BECOME A RELAtively new topic in retinal research after the basic science implicating VEGF in the disease[5–7,26] and the successful use of the drug in neovascular AMD[9] and PDR.[10] The data currently available for ROP can be considered only very low to low clinical evidence given the nonrandomized nature of the studies, especially the case reports and retrospective reviews,[27] and therefore, despite the results of these studies, the question still remains as to whether

bevacizumab should be used in the treatment of ROP. Nonetheless, the variability in the currently available reports suggest that there remains much to be studied regarding the dose and frequency of the drug, its long-term systemic effects, at what point the drug should be given, and whether bevacizumab should be used in conjunction with other therapies if it were to be used in ROP. Indeed, the heterogeneity and the lack of high-quality evidence precluded a meta-analysis at present.

For the treatment of neovascular AMD, the most commonly used dose of off-label bevacizumab is 1.25 mg,[9] and smaller monthly intravitreal injections of 0.5 mg of the approved anti-VEGF antibody fragment called ranibizumab (Lucentis; Genentech Inc) currently are in use.[28] Two published studies included in this review used 1.25 mg bevacizumab, without any ocular or systemic effects reported.[22,25] However, VEGF plays a number of critical roles in the developing retina as a survival factor for retinal neurons[29] and in maintaining the health of the retinal pigment epithelium.[30] It also influences neuronal growth and differentiation because of its neurotrophic effects[31,32] and has a critical role as a neuroprotectant in the central nervous system in the adaptive response to ischemia.[33] Therefore, it is important to preserve these essential physiologic effects of VEGF in the developing retina when treating the pathologic neovascularization in ROP. A histologic analysis included in 1 case report by Kong and associates, who used a 0.5-mg intravitreal injection of bevacizumab, did not note any inflammation or extensive apoptosis as determined by caspase-3 immunostaining.[20] Whether this holds true for larger or repeated doses of the drug remains unknown.

An additionally important issue to consider is when or even if bevacizumab should be used alone or in conjunction with other treatments such as laser photocoagulation or vitrectomy. From the limited reports reviewed here, eyes with anterior segment involvement including tunica vasculosa lentis and persistent hyaloids arteries, which preclude the application of laser treatment, have been shown to benefit consistently from intravitreal bevacizumab.[17,20,22,24] The limited visibility of the fundus that may result also has been demonstrated to resolve after intravitreal bevacizumab.[21,22,25] Clearly, with few other options in these conditions, intravitreal bevacizumab is a very attractive consideration. In contrast, patients with stage 4 disease, which involves partial RD that is extrafoveal (stage 4A) or foveal (stage 4B),[34] have had mixed outcomes. Of the 17 eyes that were documented to have stage 4 disease and were treated initially with only bevacizumab, 4 eyes experienced resolution of their condition and did not require further treatment,[23,25] 3 eyes were documented as worsening,[19,22,23] and the remaining 10 eyes subsequently were treated with surgery.[23,25] It is possible that inhibiting VEGF at this point can upset a complex interaction between VEGF, connective tissue growth factor, and transforming growth factor in angiogenic and fibrotic tissue,[35] inducing an undesirable tissue contraction, as observed in 1 case in this review.[19] Furthermore, it is also possible that intravitreal bevacizumab would be a beneficial adjunct to vitrectomy or laser photocoagulation as performed in a few cases in this review.[18,22,23] This theoretically could prevent reproliferation after surgery; however, the lack of controls in the studies to date precludes any conclusions being made.

The actual therapeutic window in which bevacizumab would be most effective in the treatment of ROP currently is unknown. Unlike other ocular neovascular conditions like exudative AMD and PDR, where there is continual release of VEGF,[36,37] there is a single burst of VEGF that promotes neovascularization in ROP.[38] Therefore, repeat injections likely would be unnecessary if the intravitreal injection could be administered at the correct time. Sonmez and associates reported a significant increase in the intravitreal levels of VEGF in vascularly active stage 4 disease, indicating that the administration of bevacizumab should be before the onset of this increase, such as during stage 3.[39] An advantage of intravitreal anti-VEGF therapy over laser therapy is that even if it is administered after an increase in VEGF, it can inhibit the advance of the molecule already in the vitreous, whereas laser only prevents new production of VEGF.

Another important consideration in the use of bevacizumab for ROP is the potential for systemic complications. In addition to its role in angiogenesis, VEGF functions as a vasodilator in the vasculature by altering the intracellular distribution of the tight junction protein occludin[40,41] and by upregulating the production of nitric oxide in both arterioles and venules.[42,43] There have been concerns regarding the risk of cerebrovascular and myocardial events with the use of ranibizumab for AMD, and a meta-analysis has noted an association between cerebrovascular accidents and intravitreal ranibizumab injections.[44] Although bevacizumab is a full human antibody and is larger than the ranibizumab fragment, a greater 1.25-mg intravitreal dose of bevacizumab has been reported to yield a serum VEGF concentration of 3.3 μg/ml at 8 days after injection in rabbits.[45] The concentration of VEGF-A has been reported to be as high as 600 pg/ml in infants at 32 weeks postmenopausal age,[46] and therefore the concentration of bevacizumab could be much larger than the VEGF in the circulation. Moreover, infants who already have undergone laser therapy would be at higher risk for these systemic effects because of the destruction of the natural barrier of the full-thickness retina, which can increase the exit of bevacizumab from the choroidal vessels into the blood.

An ideal randomized control trial would aim to address how effective bevacizumab alone is in treating ROP in a sufficiently large cohort of patients using objective outcome measures. None of the reports to date have enrolled large numbers of patients to allow for strong statistical analyses, and the outcome measures ideally should involve visual acuity as assessed by Teller Acuity Cards[23] or the

zone, stage, and extent of the disease, if any, after treatment.[34] In addition, it also would be advantageous to evaluate how effective bevacizumab functions as an adjunct to vitrectomy in patients with stage 4 disease. Therefore, a cohort of infants should receive this surgery only and serve as a basis to compare those receiving this treatment in addition to bevacizumab. Long-term follow-up of patients receiving bevacizumab would be beneficial to discern whether interfering with VEGF has effects on the normal development of the retina or the systemic vasculature. Future studies also should aim to evaluate the cost-effectiveness in terms of the timing of delivery and how bevacizumab compares with traditional therapies at various stages of ROP.

Considerable variability exists regarding how bevacizumab is used for severe ROP even in the limited data to date. The lack of high-quality studies prevents any strong conclusions regarding the efficacy of bevacizumab for ROP, and therefore, physicians using it before further clinical trials are reported should proceed with caution and should ensure that patients are fully informed about its use. Intravitreal injection of this drug has the potential to overcome the relatively poor outcomes with laser and cryotherapy, especially for zone I and aggressive posterior ROP cases. Future studies should aim to address the optimal timing of delivery and the most effective dose. This information is of critical importance to avoid unnecessary repeated delivery and laser therapy that could increase the risk of systemic side effects. Moreover, whether additional therapy with bevacizumab is necessary remains to be determined and may depend on the stage at which treatment is initiated. The beneficial effect and advantages of bevacizumab for ROP that have been reported in the limited literature to date indicate that the randomized control trials to come are warranted.

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Biosketch

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Biosketch

Professor Andrew F. Smith, MSc, PhD, graduated from McGill University in 1992 and obtained a doctorate in public health medicine from the University of London, England in 1999. The main focus of Dr Smith's research has been the development and application of health economics and epidemiological techniques to better understand health outcomes and interventions in eye and other diseases. Currently, Dr Smith is an Adjunct Professor (Health Economics) at McGill University.