SMOKING STATUS AND TREATMENT OUTCOMES OF VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

ALEXANDER F. VITTORIO, MBBS,* VUONG NGUYEN, PHD,† DANIEL BARTHELMES, MD, PHD,‡ JENNIFER J. ARNOLD, MBBS (HONS),§ CHUI M. G. CHEUNG, MBBS,¶ NEIL MURRAY, MBCHB,** MARK C. GILLIES, MBBS, PHD† THE FIGHT RETINAL BLINDNESS! STUDY GROUP

Purpose: To assess whether smoking status affects 1-year visual outcomes in eyes treated with vascular endothelial growth factor inhibitors for neovascular age-related macular degeneration.

Methods: Retrospective analysis of data from a prospectively designed, multicenter, observational database. Nine hundred and eighty seven treatment-naive eyes of patients with neovascular age-related macular degeneration were tracked by the Fight Retinal Blindness! outcome registry in Australia, New Zealand, Singapore, and Switzerland who had documented smoking status at baseline and commenced vascular endothelial growth factor inhibitor therapy from January 2006 to December 2016. Generalized additive models were used to display visual acuity results.

Results: There was a significant difference in mean improvement in visual acuity at 12 months between nonsmokers, ex-smokers, and current smokers (7.7 vs. 6.1 vs. 3.5 letters of change; $P = 0.046$) among patients who completed 12 months of treatment when adjusted for age, baseline visual acuity, and choroidal neovascular membrane lesion type and nested for practice. There was no significant difference in the median number of injections over 12 months of treatment by smoking status. Current smokers were a mean of 6.2 years younger than nonsmokers when they started treatment ($P < 0.001$).

Conclusion: This study found inferior 12-month visual outcomes in patients who continued to smoke while receiving vascular endothelial growth factor inhibitor therapy for neovascular age-related macular degeneration.

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Age, genetic factors, and smoking are the main known risk factors for the development of age-related macular degeneration (AMD), with smoking being the major modifiable risk factor.[1–3] Smoking has consistently been associated with the pathogenesis of AMD, with proposed mechanisms including decreases in macular xanthophyll, decreased choroidal blood flow, and reduced antioxidants.[4] Nicotine may also directly potentiate subretinal inflammation and platelet-derived growth factor–mediated upregulation of endothelial smooth muscle cell proliferation.[5,6]

Although cigarette smoking is a well-documented risk factor for neovascular AMD (nAMD),[2] its impact on the efficacy of vascular endothelial growth factor (VEGF) inhibitor agents has not been firmly established. The odds ratio of developing nAMD across population based cross-sectional studies has been estimated to be 2.5 to 7.0 for smokers compared with nonsmokers.[7–12] The effect of smoking on VEGF inhibitor treatments was not analyzed in these studies. Quitting smoking reduces the risk of developing AMD, while higher-pack year smokers have >5-fold risk of developing nAMD in their second eye.[7,13]

None of the pivotal phase three studies of ranibizumab or aflibercept to treat nAMD studied smoking status as a variable for treatment response.[14–20] A single-center South Korean analysis of 125 eyes reported that current cigarette smoking was associated

with poor visual acuity improvement with VEGF inhibitors for exudative AMD, although only 14 smokers were included.[21] A subgroup analysis of 1,105 patients from the CATT study found no significant difference of mean visual acuity change at 12 months, although this was not adjusted for differences in groups at baseline.[22] The purpose of this study was to investigate the effect of smoking status on real-world outcomes of VEGF inhibitor agents for nAMD using data from the large multinational "Fight Retinal Blindness!" (FRB!) registry.

Methods

Design and Setting

This was an observational study of treatment-naive eyes from the prospectively designed FRB! registry that had received intravitreal VEGF inhibitor treatment for nAMD. The FRB! registry is a web-based multinational database where the treating ophthalmologist records patient information and treatment outcomes.[23] The number of letters read on a logarithm of the minimum angle of resolution visual acuity chart (best of uncorrected, corrected, or pinhole), treatment performed, activity of the choroidal neovascular lesion, and any procedures or adverse events were mandatorily collected at each patient visit.[23] This study was approved by the Human Research Ethics Committees of the University of Sydney, the Royal Victorian Eye and Ear Hospital, the Royal Australian and New Zealand College of Ophthalmologists, the University Hospital, Zurich, and SingHealth, Singapore. Ethics committees in Australia and New Zealand approved the use of "opt out" patient consent.

Patient Selection and Variables

We studied patients with treatment-naive nAMD from Australia, New Zealand, Singapore, and Switzerland who had documented smoking status and started treatment from January 2006 to December 2016 to allow for at least 1 year of treatment. Smoking status was determined at the time of their baseline visit and included current smokers, ex-smokers, and non-smokers. Those who continued follow-up for at least 365 days were defined as "completers," while those with less than 365 days of follow-up were "noncompleters."

Study Measurements

Patient age, smoking status, sex, visual acuity, lesion type, size, and activity were recorded at the baseline visit, which is when treatment was started. Treatments used, along with visual acuity and activity ("active" or "inactive") of choroidal neovascular membrane (CNVM), were recorded at each follow-up visit. Lesion activity status was graded by the treating ophthalmologist at each visit, with lesions graded as active if there were "features such as subretinal or intraretinal fluid or new hemorrhage that suggested that the CNV lesion was active." Idiopathic polypoidal choroidal vasculopathy was diagnosed using indocyanine green angiography.

Outcomes

The primary outcome was mean change in visual acuity after 12 months of treatment for patients with different smoking histories. Secondary outcomes included the mean change in visual acuity at 24 months, where available, the frequency of injections required for patients of different smoking histories and the proportion of visits at which the choroidal neovascularization lesion was graded as active.

Statistical Analysis

Descriptive statistics were described using the mean, SD, 95% confidence interval (CI), median, first and third quartiles (Q1, Q3), and percentages where appropriate. One-way analysis of variance, chi-square, pairwise *t*-tests, or Wilcox tests (adjusted for multiple comparisons) were used as appropriate to compare demographics between smoking groups. The visual acuity closest to the 12-month time point, or the last

From the *Department of Ophthalmology, Princess Alexandra Hospital, Brisbane, Queensland, Australia; †Discipline of Ophthalmology, Save Sight Institute, Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia; ‡Department of Ophthalmology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; §Marsden Eye Specialists, Parramatta, New South Wales, Australia; ¶Singapore National Eye Centre, Singapore, Singapore; and **Rotorua Eye Clinic, Rotorua, New Zealand.

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Reprint requests: Mark C. Gillies, MBBS, PhD, Save Sight Institute, South Block, 8 Macquarie Street, Sydney, NSW 2000, Australia; e-mail: mark.gillies@sydney.edu.au

observation carried forward for noncompleters, was used as the visual acuity at 12 months for cross-sectional analyses and to present raw, unadjusted outcomes, including mean visual acuity change, the proportion of eyes gaining or losing >10 letters, and the proportion of eyes with visual acuity >70 or <35 letters. Generalized additive models were used to display the visual acuity throughout the follow-up and included longitudinal data from both completers and noncompleters.

Cross-sectional analysis of mean visual acuity improvement at 12 and 24 months between smoking status groups was analyzed using mixed-models controlling for the possible confounders of age, lesion type, and visual acuity at baseline, with nesting of eyes within patients (for bilateral disease) and patients within practices. This was followed by post hoc pairwise comparisons between smoking groups. A comparison of the visual acuity curves over time using longitudinal generalized additive models including data from completers and noncompleters was also performed. The same confounding variables were included in the model, with additional random slope and intercept terms for repeated measurements in each eye. Time to first inactive CNVM grading was plotted using Kaplan–Meier survival analysis while the proportion of visits in which the lesion was graded as active was compared using logistic regression. The number of injections received was analyzed using Poisson regression.

The Holm–Bonferroni correction was used for all pairwise comparisons. All analyses were performed using R version 3.4.3.[24]

Results

Patient Characteristics

Data from 987 eyes from 837 patients recorded at 43 participating practices within Australia, New Zealand, Singapore, and Switzerland initiating treatment with VEGF inhibitors between January 2006 and December 2016 were included in the analysis. Of these, 756 eyes (77%) completed at least 12 months of follow-up. Current smokers were a mean of 6.2 years younger at presentation than nonsmokers ($P < 0.001$; Table 1). The baseline visual acuity and lesion size on fundus fluorescein angiography or optical coherence tomography were significantly different between smoking groups; smokers had lower visual acuity and larger lesions at baseline (Table 1). There was no significant difference in the initial VEGF inhibitor used between the different groups (Table 1). Treatment frequency

Table 1. Baseline Demographics by Smoking Status

	All Patients	Nonsmoker	Ex-smoker	Smoker	*P*
Eyes, no. (%)	987	594 (60.1)	265 (26.8)	128 (13.0)	
Patients, no. (%)	837	502 (60.0)	232 (27.7)	103 (12.3)	
Female, no. (%)	577 (58.5)	422 (71)	108 (40.8)	47 (36.7)	<0.001*
Age, mean (SD)	77.4 (8.9)	78.3 (9)	78.1 (8.5)	72.1 (7.4)	<0.001†
Baseline VA, mean letters (SD)	56.7 (20.6)	56 (20.9)	59.3 (18.9)	54.5 (22.0)	0.036†
Initial VEGF inhibitor					
Ranibizumab, no. (%)	434 (44.0)	262 (60.4)	122 (28.1)	50 (11.5)	0.744*
Bevacizumab, no. (%)	322 (32.6)	196 (60.9)	81 (25.2)	45 (14.0)	
Aflibercept, no. (%)	231 (23.4)	136 (58.9)	62 (26.8)	33 (14.3)	
CNVM lesion size					
CNVM size, median μm	2,300	2,227.5	2,336	2,515.5	0.032†
CNVM size, Q1–Q3	1,498.5–3,705	1,420.5–3,582.2	1,500–3,576	1,582–4,198.5	
CNVM lesion type					
Occult, no. (%)	484 (49.0)	317 (65.5)	113 (23.3)	54 (11.2)	0.001*
IPCV, no. (%)	132 (13.4)	76 (57.6)	29 (22.0)	27 (20.5)	
Minimally classic, no. (%)	71 (13.4)	38 (53.5)	22 (31.0)	11 (15.5)	
Predominantly classic, no. (%)	157 (15.9)	75 (47.8)	63 (40.1)	19 (12.1)	
Other, no. (%)	66 (6.7)	40 (60.6)	17 (25.8)	9 (13.6)	
Not done, no. (%)	77 (7.8)	48 (62.3)	21 (27.3)	8 (10.4)	
Country					
Australia (%)	471 (47.7)	276 (58.6)	159 (33.7)	36 (7.6)	
Switzerland (%)	203 (20.6)	128 (63.1)	26 (12.8)	49 (24.1)	
Singapore (%)	195 (19.8)	121 (62.1)	40 (20.5)	34 (17.4)	
New Zealand (%)	118 (12.0)	69 (58.5)	40 (33.9)	9 (7.6)	

*Chi-squared test.
†Analysis of variance.
VA, visual acuity.

was also analyzed to reflect the treatment regimen. We found 66.2% of patients had a treatment regimen consistent with treat and extend (received an injection in >80% of visits), while 33.8% had a regimen consistent with pro re nata (received an injection in ≤80% of visits).

Treatment Effect Based on Smoking Status

Visual acuity for all groups combined improved by a raw mean of 5.9 letters of change (4.9–6.9 95% CI) over 12 months. There was a significant difference in adjusted mean improvement in visual acuity at 12 months between nonsmokers, ex-smokers, and smokers for completers and noncompleters combined (8.0 vs. 5.9 vs. 4.6 letters of change, respectively; P = 0.040) (Table 2). A significant difference in adjusted mean improvement was also seen when only completers where analyzed (7.7 vs. 6.1 vs. 3.5 letters of change, respectively; P = 0.046). Pairwise comparison between groups did not clearly define which pairs differed significantly.

The modeled visual acuity curves over 12 months of the different groups were significantly different ($P <$ 0.001) (Figure 1), indicating different treatment trajectories between the groups. The median number of treatments over 12 months was the same for all 3 groups (Table 2). Visual outcome after 24 months was available in 538 of the 758 patients included in the 12-month analysis. The smoker group (n = 68) still had numerically lower visual gain, although the difference was not statistically significant. Nonsmokers, ex-smokers, and smokers gained 6.7 v 5.2 v 3.7 letters of change, respectively, over 24 months (P = 0.134). Despite this, the modeled curves of visual acuity measurements over 24 months were significantly different among the three groups ($P < 0.001$) (Figure 1).

Kaplan–Meier survival analysis of the proportion of patients with active CNVM showed a trend of nonsmokers being graded as inactive sooner than ex-smokers or smokers (Figure 2). Median time after starting treatment to when the CNVM was first graded as inactive did not differ significantly between nonsmokers, ex-smokers, and smokers (99 v 91 v 111 days; P = 0.153) (Table 2).

Table 2. Outcome Measures at 12 Months by Completer Status and Smoking Status

	All Patients	All Patients by Smoking Status				Completers (n = 756)				Noncompleters (n = 231)			
	All Patients (n = 987)	Nonsmokers, n = 594	Ex-smokers, n = 265	Smokers, n = 128	P	Nonsmokers, n = 457	Ex-Smokers, n = 197	Smokers, n = 102	P	Nonsmokers, n = 137	Ex-Smokers, n = 68	Smokers, n = 26	P
Mean baseline VA (SD)	56.7 (20.6)	56 (20.9)	59.3 (18.9)	54.5 (22.0)	0.036	57.5 (20.0)	61.1 (17.3)	55.3 (21.3)	0.030	50.8 (22.8)	54.3 (22.5)	51.2 (24.9)	0.585
Mean 12 month VA (SD)	62.6 (21.6)	62.6 (21.5)	63.6 (20.6)	60.3 (24.1)	0.373	64.5 (19.8)	66.0 (18.0)	60.3 (24.4)	0.060	56.2 (25.3)	56.6 (25.7)	60.7 (23.7)	0.711
Mean 12 month VA change (95% CI)	5.9 (4.9–6.9)	6.6 (5.3–7.9)	4.3 (2.4–6.1)	5.9 (2.6–9.1)	0.147	7 (5.5–8.5)	4.9 (2.9–7.0)	4.9 (1.2–8.7)	0.233	5.4 (2.6–8.3)	2.3 (−1.9–6.5)	9.5 (3.2–15.8)	0.164
Adjusted 12 month VA change (95% CI)		8.0 (6.0–10.0)	5.9 (3.4–8.3)	4.6 (1.5–7.8)	0.042	7.7 (5.7–9.6)	6.1 (3.6–8.6)	3.5 (0.1–6.9)	0.047	7.2 (3.1–11.4)	3.3 (−1.6–8.2)	6.4 (−0.4–13.2)	0.283
Gain VA >10 letters (%)	36.8	36.2	34.3	44.5		36.8	35.5	45.1		34.3	30.9	42.3	
Loss VA >10 letters (%)	8.9	8.1	9.8	10.9		7.4	9.6	11.8		10.2	10.3	7.7	
VA >70, % (baseline/final)	32.1/53.1	32.0/53.2	35.8/52.8	25.0/53.1		33.9/55.1	37.6/55.8	24.5/52.9		25.5/46.7	30.9/44.1	26.9/53.8	
VA <35% (baseline/final)	15.7/13.7	16.5/13.5	11.7/11.3	20.3/19.5		13.3/10.7	9.6/8.6	18.6/19.6		27.0/22.6	17.6/19.1	26.9/19.2	
Median 12 month injections (IQR)	7 (5–9)	7 (5–9)	7 (4–9)	7 (5–10)	0.845	8 (6–10)	8 (6–10)	7 (5–10)	0.559	5 (3–7)	4 (2.8–6)	5.5 (3.2–8)	0.051
Lesion active visits, %	60.1	59.6	56.3	68.2		59	56.1	69.2		62.7	57.2	63.1	
Median time to inactivity, days (95% CI)		99 (91–114)	91 (83–112)	111 (92–161)	0.283								

Adjusted using mixed-models controlling for the possible confounders of age, lesion type, and VA at baseline, with nesting of eyes within patients (for bilateral disease) and patients within practices.
VA, visual acuity.

Discussion

This analysis on the effect of smoking on outcomes of treatment of nAMD found significant differences between smoking groups for age, baseline visual acuity, and baseline CNVM size when they started treatment. The younger age of smokers is likely to be due to current smokers having an up to 7-fold

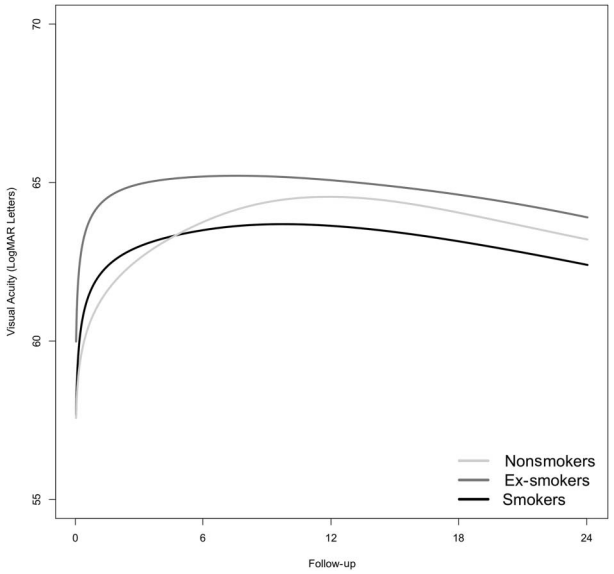

Fig. 1. Generalized additive model of visual acuity over first 24 months of VEGF inhibitor treatment by smoking status.

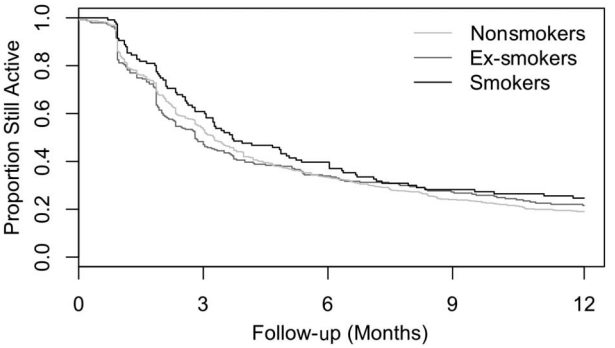

Fig. 2. Kaplan–Meier estimator of proportion of patients with lesions still active over time dependent on smoking status.

increased risk of developing nAMD than nonsmokers.[7,11] Despite being younger, these patients also seemed to have more aggressive disease, with worse baseline visual acuity and larger CNVM. This result is consistent with a Welsh study that also investigated smoking and VEGF inhibitors.[25] Men were relatively overrepresented in both the ex-smoker and smoker cohorts in our study, which is consistent with worldwide prevalence rates of smoking for men (31.1%–48.6%) and women (6.2%–11.3%).[26–28] Female smokers have also been estimated to smoke 20% less cigarettes a day than male smokers.[29] This is particularly meaningful in the setting of the established dose–response effect of pack-years and subsequent progression of nAMD.[13,30–32] Of concern, a recent British study reported that only 53.1% of smokers with AMD recalled that they were advised to quit smoking by their ophthalmologist or optometrist.[33]

The adjusted mean visual acuity improvement at 12 months was significantly different among the three groups. Nonsmokers had more than twice the gain in visual acuity after 12 months than smokers. Despite this, we were not able to determine with confidence which pairs differ significantly. The same pattern was observed in the 3 groups at 24 months, although the difference between adjusted mean visual acuity change was not statistically significant. Despite the known "ceiling effect" of eyes with better baseline visual acuity having less room to improve, nonsmokers had better visual acuity gains even when they had better baseline visual acuity. The differences in the modeled curves of the mean visual acuity change over 12 month and 24 months were also statistically significant. Quitting smoking may lead to better visual outcomes after 1 year of treatment, since ex-smokers gained a mean of 6.1 letters versus 3.5 letters for smokers, but further studies would be required to determine whether this association is statistically significant.

The outcomes we found in smokers receiving VEGF inhibitors add to a pool of varied results from other studies. The Comparison of Age-related Macular Degeneration Treatments Trials (CATT) presented cohort outcomes for ranibizumab or bevacizumab at 12 months for 1,105 patients dependent on smoking status.[22] They found no statistically significant effect of smoking, although they did not adjust for baseline age, baseline visual acuity, and type or size of CNVM, all of which were associated with significant differences in outcomes in their data, as well as our own.[22] The 5-year follow-up analysis of the CATT cohort, however, reported smoking was significantly and independently associated with worse long-term vision outcomes.[34] Two Korean studies investigated the prevalence of smokers in those who were poor responders to VEGF inhibitors but found contrasting results.[21,35] A relatively small Japanese case–control study of 64 eyes found no effect of smoking on outcomes of treatment with ranibizumab or aflibercept, although they reported significant central retinal thinning in smokers.[36] A prospective U.K. study of 106 eyes found similar absolute values for each group but was not statistically significant.[37] An Italian study of ranibizumab usage found better visual outcomes in never smokers by five letters.[38] The strengths of our methods were the use of a real world database, as well as adjusting for significant confounders such as baseline visual acuity.

The mechanism of any potential association between current smokers and poorer visual outcomes with VEGF inhibitors is unclear. A genetic background may aggravate the detrimental effect that smoking has on treatment outcomes for nAMD.[39] Whole genome sequencing has associated many single

nucleotide polymorphisms with AMD, including complement factor H,[37,40,41] age-related maculopathy susceptibility-2 (ARMS2),[42] and high-temperature requirement A-1.[37,42] Combining previous smoking history with these "at-risk" alleles has been reported to account for up to a 8-letter difference in visual outcomes.[38] Smokers homozygous for the at-risk complement factor H allele have a reported odds ratio of 8.7 to 34.5 for late AMD,[43,44] while smokers homozygous for ARMS2 have an estimated OR of 8.2 to 23.3.[43–45] Similarly, it has been suggested that smoking history in combination with complement factor H and ARMS2 mutations confers a greater risk than each factor alone.[44] The increased time to CNVM inactivity found in current smokers did not reach statistical significance. Cigarette smoking causing an increase in autophagic flux and thereby further degradation of the retinal pigment epithelium has been suggested as a causative mechanism in recent studies.[46] Smoking history has also been associated with decreased mean central macular choroidal thickness.[47] A prospective study analyzing the effect of smoking status on central macular choroidal thickness, persistence of subretinal fluid, and visual acuity in VEGF inhibitor–treated nAMD may clarify the causal mechanism of decreased treatment efficacy.

There are some limitations to our study. The 12-month dropout rate of 23% was typical of observational studies but still high. The mean visual acuity change at the last observed visit for dropouts was still quite good, suggesting many eyes may have been lost to follow-up due to reasons unrelated to treatment outcomes such as going to another doctor, as we have previously reported in an analysis of participants in this database.[48] We did not distinguish between bevacizumab, ranibizumab, and aflibercept since the analysis included data before the introduction of aflibercept in 2012 to 2013, although real-world studies have reported similar outcomes between these drugs.[49–51] Measurement of smoking status as current, ex-smoker, or nonsmoker rather than utilization of pack-years did not allow for establishment of any dose–response relationship. Nor was it known when ex-smokers quit; some patients may have quit more recently than others or taken up smoking again during the follow-up period. Regardless, ex-smokers were observed to achieve intermediate outcomes between nonsmokers and smokers.

To conclude, we have collated data over 11 years of treatment of nAMD from multiple practices and countries. The adjusted visual acuity change at both 12 months and 24 months consistently found less improvement for current smokers than for never smokers, with past smokers in between. Curves modeling visual acuity also showed a highly significant difference in visual acuity outcomes over the 24 months of treatment dependent on smoking status. Although some small reports have found no such association, our study complements others that have linked smoking with inferior nAMD treatment outcomes. This may be used as an extra inducement for smokers to quit when they start treatment.

Key words: aflibercept, AMD, bevacizumab, cigarette, ranibizumab, nicotine.

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