CJO JCO

Original Article

# Patterns of anti-vascular endothelial growth factor discontinuation in neovascular age-related macular degeneration



Amy Basilious, MD, Bobbi Smuck, CCRPC, Julie Duncan, BA, CCRPC, Monali S. Malvankar-Mehta, PhD, Verena R. Juncal, MD, FRCSC, Phil Hooper, MD, FRCSC, Tom G. Sheidow, MD, FRCSC

***Objective:*** To report on anti−vascular endothelial growth factor (anti-VEGF) discontinuation in neovascular age-related macular degeneration (nAMD).

***Design:*** Retrospective cohort study.

***Participants:*** Treatment-naive nAMD patients initiating anti-VEGF injections between 2015 and 2021.

***Methods:*** Demographics, treatment start and end dates, number of injections, treatment length, reason for discontinuation, and baseline and final data (i.e., age, best-corrected visual acuity, and central subfield thickness) were recorded. Statistical analyses using STATA 17.0 assessed differences between baseline and final values and between treatment-discontinuation subgroups.

***Results:*** A total of 619 eyes of 502 treatment-naive patients (9015 injections) were included (age, 81.6 ± 8.4 years; 64.0% female). Discontinuation rate was 58.3% (361 of 619), with 310 patients discontinuing because of the lack of visual benefit (n = 152), severe comorbidity or death (n = 82), transferred (n = 33), stable off active treatment (n = 19), lack of benefit plus stable off treatment (n = 14), patient decision (n = 6), and ocular comorbidity (n = 4). Among the 309 remaining patients, 51 (16.5%) were lost to follow-up. Discontinuation occurred within the first year in 49.3% (n = 178). Visual acuity was at least maintained in all groups and improved in the following groups: severe comorbidity or death ($p < 0.0001$), lost to follow-up ($p = 0.0003$), transferred ($p = 0.0004$), and stable off treatment ($p = 0.0053$). The lack of visual benefit group had no improvement in vision regardless of treatment length. Compared with other subgroups, those stable off treatment group was younger ($p = 0.0055$), had better baseline vision ($p = 0.0018$), received more injections ($p = 0.0437$) over a longer time ($p = 0.0034$), and achieved better final vision ($p < 0.0001$).

***Conclusion:*** While there was a high discontinuation rate over 7.5 years, most were attributable to disease or treatment factors and non-modifiable patient factors. Discontinuation frequently occurred within the first year.

***Objectif:*** Faire un compte-rendu sur l'abandon du traitement par un anti-VEGF (facteur de croissance endothélial vasculaire) dans la dégénérescence maculaire liée à l'âge (DMLA) néovasculaire.

***Nature:*** Étude de cohorte rétrospective.

***Participants:*** Patients présentant une DMLA néovasculaire jamais traitée qui ont commencé à recevoir des injections d'anti-VEGF entre 2015 et 2021.

***Méthodes:*** Ont été enregistrées les variables suivantes **:** données démographiques, date de début et de fin du traitement, nombre d'injections, durée du traitement, raison de l'abandon du traitement, valeurs de départ et valeurs finales (soit l'âge, la meilleure acuité visuelle corrigée et l'épaisseur du sous-champ central). Les analyses statistiques, qui ont fait appel au logiciel STATA 17.0, mesuraient les différences entre les valeurs de départ et les valeurs finales de même qu'entre les sous-groupes de patients qui ont abandonné le traitement.

***Résultats:*** Au total, 619 yeux de 502 patients jamais traités (9015 injections) ont été inclus (âge : 81,6 ± 8,4 ans; 64,0 % de femmes). Le taux d'abandon du traitement était de 58,3 % (361 sur 619), dont 310 patients qui ont mis fin à leur traitement pour les motifs suivants : absence de bienfait sur le plan visuel (n = 152), comorbidité grave ou décès (n = 82), transfert à une autre équipe de soins (n = 33), état stable sans traitement actif (n = 19), absence de bienfait du traitement et état stable sans traitement actif (n = 14), choix du patient (n = 6) et comorbidité oculaire (n = 4). Parmi les 309 patients restants, 51 (16,5 %) ont été perdus de vue pendant le suivi. L'abandon du traitement est survenu pendant la première année dans 49,3 % des cas (n = 178). L'acuité visuelle s'est au moins maintenue chez tous les patients et s'est améliorée dans les sous-groupes suivants: comorbidité grave ou décès ($p < 0,0001$), perte de vue pendant le suivi ($p = 0,0003$), transfert à une autre équipe de soins ($p = 0,0004$) et état stable sans traitement actif ($p = 0,0053$). Aucune amélioration de la vision n'a été observée chez les patients du sous-groupe « absence de bienfait sur le plan visuel », peu importe la durée du traitement. Comparativement à d'autres sous-groupes, les patients dont l'état était stable sans traitement actif étaient plus jeunes ($p = 0,0055$), avaient une meilleure vision initiale ($p = 0,0018$), ont reçu un plus grand nombre d'injections ($p = 0,0437$) ou pendant plus longtemps ($p = 0,0034$) et avaient une meilleure vision finale ($p < 0,0001$).

***Conclusion:*** On a noté un fort taux d'abandon du traitement lors de la période d'évaluation de 7,5 ans. La plupart des abandons tenaient à la présence de facteurs pathologiques ou thérapeutiques ou encore à des facteurs non modifiables inhérents aux patients. L'abandon est souvent survenu pendant la première année de traitement.

https://doi.org/10.1016/j.jcjo.2023.02.006
ISSN 0008-4182

Anti–vascular endothelial growth factor (anti-VEGF) is the mainstay of therapy for several visually debilitating diseases. Neovascular age-related macular degeneration (nAMD) patients typically require ongoing therapy to maintain efficacy, and adherence is important for optimal outcomes.

Treatment discontinuation rates in real-world studies are higher than in clinical trials.[1] Reported rates vary, with most ranging between 40% and 50%.[2,3] A recent review found that treatment was discontinued within 2 years in up to half of nAMD patients.[4] Several reasons have been cited, including disease and patient factors such as patient preference, loss to follow-up, and death. Frequent injections come with significant burdens on patients and caregivers, compounded by the challenges of the disease itself.[5–8] Nonadherence to treatment is a known concern.[4,6,9] COVID-19 posed additional challenges for physicians and patients, resulting in poorer outcomes due to deferred treatment.[10,11]

There have been numerous different approaches to discussing adherence to and persistence with intravitreal therapy. A framework for defining these concepts was recently developed to improve reporting on the use of anti-VEGF injections.[12] Short-term *nonadherence*, defined as visits delayed by at least 2 weeks, was distinguished from longer-term *nonpersistence*, *planned discontinuation*, and *transfer of care*[12] Much of the literature has focused on prevalence and risk factors for nonadherence, but fewer studies have reported on treatment discontinuation. This study seeks to characterize anti-VEGF discontinuation patterns in nAMD patients over 7.5 years, capturing treatment patterns before and during the pandemic. We report on treatment discontinuation rate, identify key reasons, and assess variables contributing to discontinuation.

## Methods

### Study population

This was a retrospective study of all treatment-naive nAMD patients initiating therapy with anti-VEGF (aflibercept, bevacizumab, or ranibizumab) by a single surgeon (T. S.) between January 1, 2015, and June 30, 2021, in an academic tertiary centre in southwestern Ontario. Follow-up data until June 30, 2022, were included to ensure a minimum of 1 year since treatment initiation. Exclusion criteria included prior injections and peripapillary choroidal neovascularization because the treatment protocol differs from that for other nAMD types.[13] The study was approved by the Western University Health Sciences Research Ethics Board.

### Data collection

The medical record was accessed to record sex, hometown, and the following baseline and final data for each affected eye: age, best-corrected visual acuity (BCVA), fellow eye BCVA, and central subfield thickness (CST). BCVA was measured using a Snellen eye chart with current spectacle correction. BCVA was converted to logMARs. CST was defined as the automated internal limiting membrane to retinal pigment epithelium (ILM-RPE) thickness measurement from Cirrus (Carl Zeiss Meditec AG, Jenna, Germany) and Triton (Topcon, Livermore, Calif.) optical coherence tomography (OCT) reports. Baseline and final data were collected from the dates of the first and last injections, respectively. Number of injections was recorded, and the length of treatment was computed from treatment start and end dates. Distance from hometown to London, Ontario, where the centre is located, was determined.

### Reasons for discontinuation

Reasons for discontinuation were categorized as lack of visual benefit, stable off active treatment, lack of visual benefit plus stable off treatment, lost to follow-up, severe comorbidity or death, ocular comorbidity, transferred, and patient decision. Lack of visual benefit was defined as patients in whom further therapy was deemed futile by the treating physician due to macular atrophy, hemorrhage, or a lack of visual acuity improvement in a patient with little to no central acuity at baseline. Stable disease was defined as the absence of macular edema on OCT when the patient had been extended beyond 3 months from the last injection (often after missing an appointment). If patients had a lack of visual benefit and stability on OCT, they were categorized as lack of visual benefit plus stable off treatment.

Patients were lost to follow-up if they (*i*) received an injection on their last visit, (*ii*) did not attend their next appointment with no documented reason, or (*iii*) did not present for care again for the remainder of the study period. Cases were categorized as severe comorbidity or death based on notes in the clinic's medical record documenting the patient's death or attributing discontinuation to the patient developing dementia, cancer, stroke, and so on. Because some patients discontinuing due to severe comorbidity or death could have been missed with this method, the hospital medical record was also cross-referenced for cases in which the patient did not attend his or her scheduled follow-up. Ocular comorbidity was defined as other ocular conditions (e.g., other retinal disease, glaucoma, and so on) causing poor vision or injection-related endophthalmitis leading to treatment discontinuation. Cases were categorized as transferred when patients were referred by the current treating physician to an ophthalmologist in another city. Patient decision was identified as the discontinuation reason for cases in which the patient elected to stop injections.

### Statistical analysis

Discontinuation rate was defined as the proportion of eyes discontinuing injections permanently during the study period. The frequency of each discontinuation reason was determined over the whole study period and by year.

**Table 1—Demographic and clinical variables of eyes treated with anti-VEGF injections**

| Variable | Treatment ongoing | Treatment discontinued | Lack of visual benefit | Severe comorbidity or death | Lost to follow-up | Transferred | Stable off active treatment | Lack of visual benefit plus stable off treatment | Patient decision | Ocular comorbidity |
|---|---|---|---|---|---|---|---|---|---|---|
| No. of eyes | 258 | 361 | 150 | 82 | 51 | 33 | 19 | 14 | 6 | 4 |
| No. of females (%) | 171 (66.3) | 225 (62.3) | 104 (69.3) | 50 (61.0) | 29 (56.9) | 17 (51.5) | 13 (68.4) | 9 (64.3) | 1 (16.7) | 1 (25.0) |
| Baseline age, y | 79.1 ± 8.3 | 81.6 ± 8.4 | 81.4 ± 7.9 | 83.9 ± 7.1 | 82.4 ± 7.4 | 81.7 ± 7.9 | 72.7 ± 14.7 | 78.5 ± 9.6 | 85.5 ± 5.9 | 80 ± 7.4 |
| Final age, y | 82.2 ± 8.2 | 83.1 ± 8.4 | 82.5 ± 7.8 | 86 ± 7.1 | 83.6 ± 7.4 | 83 ± 7.6 | 74.9 ± 14.8 | 79.8 ± 10.2 | 86.7 ± 5.2 | 84 ± 8.2 |
| Baseline VA, logMAR | 0.6 ± 0.4 | 1.0 ± 0.5 | 1.3 ± 0.5 | 0.6 ± 0.3 | 0.9 ± 0.5 | 0.7 ± 0.4 | 0.6 ± 0.6 | 1.1 ± 0.5 | 1.1 ± 0.5 | 0.4 ± 0.1 |
| Final VA, logMAR | 0.4 ± 0.3 | 0.9 ± 0.5 | 1.3 ± 0.4 | 0.5 ± 0.4 | 0.7 ± 0.4 | 0.5 ± 0.4 | 0.3 ± 0.3 | 0.9 ± 0.4 | 0.9 ± 0.6 | 0.4 ± 0.3 |
| Baseline VA fellow eye, logMAR | 0.6 ± 0.6 | 0.6 ± 0.6 | 0.5 ± 0.6 | 0.8 ± 0.7 | 0.6 ± 0.5 | 0.7 ± 0.7 | 0.4 ± 0.4 | 0.7 ± 0.7 | 0.8 ± 0.8 | 0.6 ± 0.4 |
| Final VA fellow eye, logMAR | 0.6 ± 0.7 | 0.5 ± 0.6 | 0.5 ± 0.6 | 0.6 ± 0.7 | 0.6 ± 0.5 | 0.4 ± 0.5 | 0.4 ± 0.6 | 0.7 ± 0.7 | 0.4 | 0.9 ± 0.8 |
| Baseline CST, $\mu$m | 355.6 ± 155.6 | 364.2 ± 129.9 | 376.4 ± 143.3 | 359.8 ± 120.5 | 354.9 ± 127.1 | 337.7 ± 110.4 | 322.3 ± 90.2 | 418.1 ± 146.1 | 366.2 ± 59 | 336.8 ± 48.4 |
| Final CST, $\mu$m | 239.5 ± 60.5 | 247.1 ± 82.8 | 241.5 ± 79.4 | 246.1 ± 87.6 | 241.7 ± 55.3 | 292.3 ± 97.7 | 226.9 ± 47.3 | 254.1 ± 134.1 | 241.8 ± 25.8 | 202.8 ± 69.9 |
| No. of injections | 20.2 ± 10.9 | 10.6 ± 7.3 | 9.0 ± 5.3 | 13.6 ± 8.5 | 9.6 ± 8.0 | 10.2 ± 8.2 | 12.1 ± 4.5 | 10.0 ± 5.5 | 9.7 ± 8.7 | 27.8 ± 6.7 |
| Treatment length, y | 3.3 ± 1.8 | 1.5 ± 1.3 | 1.1 ± 0.9 | 2.0 ± 1.5 | 1.3 ± 1.3 | 1.4 ± 1.4 | 2.3 ± 1.6 | 1.3 ± 1.1 | 1.1 ± 1.2 | 3.7 ± 0.9 |
| Distance from home, km | 34.1 ± 39.7 | 36.1 ± 44.3 | 30.7 ± 40.6 | 29.9 ± 35.5 | 31.0 ± 38.4 | 92.0 ± 57.3 | 29.0 ± 34.4 | 16.8 ± 21.1 | 26.6 ± 39.5 | 79.8 ± 78.4 |

VA, visual acuity; CST, central subfield thickness.
*Note:* Continuous parameters are reported as mean ± standard deviation.

Demographic and clinical variables were reported as mean and standard deviation or frequency. The data have a non-normal distribution (Shapiro–Wilk test). The Wilcoxon rank-sum (Mann–Whitney) test was used to analyze variables across groups, and the Wilcoxon signed-rank test was used to analyze baseline and final variables within groups. Kaplan–Meier survival curves were generated for time to discontinuation. Analyses were performed using STATA version 17.0 (STATA Corporation, College Station, Tex.).

## Results

### Study population

A total of 619 eyes of 502 treatment-naive nAMD patients started treatment with anti-VEGF between January 2015 and June 2021. Mean baseline age was 81.6 ± 8.4 years, and 64.0% of patients (396 of 619) were female. Mean baseline BCVA was 0.8 ± 0.5 logMAR (Snellen equivalent 20/125). A total of 9015 injections were given, with 23.3% of patients (117 of 502) receiving injections in both eyes at some point during the study period.

### Treatment discontinuation rate

Treatment was discontinued in 361 eyes (58.3%), with 310 of these discontinued for the following reasons: 152 due to lack of visual benefit, 82 due to severe comorbidity or death, 33 transferred, 19 stable off active treatment, 14 due to lack of visual benefit plus stable off treatment, 6 due to patient decision, and 4 due to ocular comorbidity. Among the 309 remaining eyes, 51 (16.5%) were lost to follow-up. Demographic and clinical variables are reported in Table 1.

Table 2 displays the reasons for discontinuation by year. Lack of visual benefit was the most common reason in all years except 2015 and 2021. All eyes discontinued in 2015 were on treatment for <1 year because patients were treatment naive at the start of the study period. This accounts for the small number of treatment discontinuations (n = 8) and different pattern of reasons. In 2021, severe comorbidity or death was the most common reason. The year 2021 accounted for 30.5% of patients (25 of 82) stopping due to severe comorbidity or death over the 7.5 years. Severe comorbidity or death was second most common in other years. The year 2020 was an exception, where lost to follow-up was second. This corresponded to the onset of the COVID-19 pandemic and accounted for 23.5% of patients lost to follow-up (12 of 51) over the total study period.

### Visual acuity and CST

In eyes with ongoing treatment, mean BCVA improved from 0.6 ± 0.4 logMAR (Snellen 20/125) at baseline to 0.4 ± 0.3 logMAR (Snellen 20/50) at the most recent injection ($p < 0.0001$). BCVA improved in eyes with treatment discontinued from 1.0 ± 0.5 logMAR (Snellen 20/200) to 0.9 ± 0.6 logMAR (Snellen 20/160; $p < 0.0001$). The

**Table 2—Frequency of reasons for discontinuation by treatment end year**

| Treatment end year | Reason for treatment discontinuation, n (% of year total) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Lack of visual benefit | Severe comorbidity or death | Lost to follow-up | Transferred | Stable off active treatment | Lack of visual benefit plus stable off treatment | Patient decision | Ocular comorbidity |
| 2015 (n = 8) | 1 (12.5) | 1 (12.5) | 1 (12.5) | 3 (37.5) | 0 | 1 (12.5) | 1 (12.5) | 0 |
| 2016 (n = 32) | 15 (46.9) | 7 (21.9) | 4 (12.5) | 3 (9.4) | 1 (3.1) | 2 (6.3) | 0 | 0 |
| 2017 (n = 55) | 27 (49.0) | 9 (16.4) | 9 (16.4) | 6 (10.9) | 3 (5.5) | 0 | 1 (1.8) | 0 |
| 2018 (n = 51) | 21 (41.2) | 13 (25.5) | 9 (17.7) | 4 (7.8) | 0 | 3 (5.9) | 1 (2.0) | 0 |
| 2019 (n = 60) | 29 (48.3) | 14 (23.3) | 8 (13.3) | 2 (3.3) | 3 (5.0) | 2 (3.3) | 0 | 2 (3.3) |
| 2020 (n = 63) | 24 (38.1) | 10 (15.9) | 12 (19.1) | 5 (7.9) | 6 (9.5) | 2 (3.2) | 1 (1.6) | 2 (3.2) |
| 2021 (n = 73) | 24 (32.9) | 25 (34.3) | 7 (9.6) | 9 (12.3) | 2 (2.7) | 3 (4.1) | 2 (2.7) | 0 |
| 2022 (Jan–July) (n = 19) | 9 (47.4) | 3 (15.8) | 1 (5.3) | 1 (5.3) | 4 (21.1) | 1 (5.3) | 0 | 0 |

following subgroups also experienced BCVA improvements: severe comorbidity or death (0.6 ± 0.3 to 0.5 ± 0.4 logMAR; $p < 0.0001$), lost to follow-up (0.9 ± 0.5 to 0.7 ± 0.4 logMAR; $p = 0.0003$), transferred (0.7 ± 0.4 to 0.5 ± 0.4 logMAR; $p = 0.0004$), and stable off active treatment (0.6 ± 0.6 to 0.3 ± 0.3 logMAR; $p = 0.0053$). There was no significant improvement in the following subgroups: lack of visual benefit, lack of visual benefit plus stable off treatment, patient decision, and ocular comorbidity.

In eyes with ongoing treatment, mean CST improved from 355.6 ± 155.6 $\mu$m at baseline to 239.5 ± 60.5 $\mu$m at the most recent injection ($p < 0.0001$). CST improved in eyes with treatment discontinued due to lack of visual benefit (baseline, 375.9 ± 143.6 $\mu$m to final, 243.9 ± 81.7 $\mu$m; $p < 0.0001$), lack of visual benefit and stable off treatment (418.1 ± 146.1 to 254.1 ± 134.1 $\mu$m; $p = 0.0043$), stable off active treatment (322.3 ± 90.2 to 226.9 ± 47.3 $\mu$m; $p = 0.0004$), severe comorbidity or death (359.8 ± 120.5 to 246.1 ± 87.6 $\mu$m; $p < 0.0001$), lost to follow-up (354.9 ± 127.1 to 241.7 ± 55.3 $\mu$m; $p < 0.0001$), and transferred (337.7 ± 110.4 to 292.3 ± 97.7 $\mu$m; $p = 0.0084$).

## Treatment length and interval

The mean treatment length was 3.3 ± 1.8 years in those with treatment ongoing and 1.5 ± 1.3 years in those with treatment discontinued ($p < 0.0001$). Treatment length was <2 years in all discontinuation subgroups except severe comorbidity or death (2.0 ± 1.5 years), stable off active treatment (2.3 ± 1.6 years), and ocular comorbidity (3.7 ± 0.9 years). Treatment was discontinued within the first year in 49.3% (178 of 361). Figure 1 displays Kaplan–Meier survival curves for time to discontinuation by subgroup.

Among the lost to follow-up and patient decision groups (n = 57), discontinuation most often occurred at a treatment interval of 4–5 weeks (n = 17; 19.8%) or ≥12 weeks (n = 17; 19.8%). Of the 23 remaining, 8 stopped at a 6- to 7-week treatment interval, 9 at an 8- to 9-week interval, and 6 at a 10- to 11-week interval.

## Distance from hometown

Figure 2 displays the distribution of patients' hometowns in relation to London, Ontario, where the centre is located.

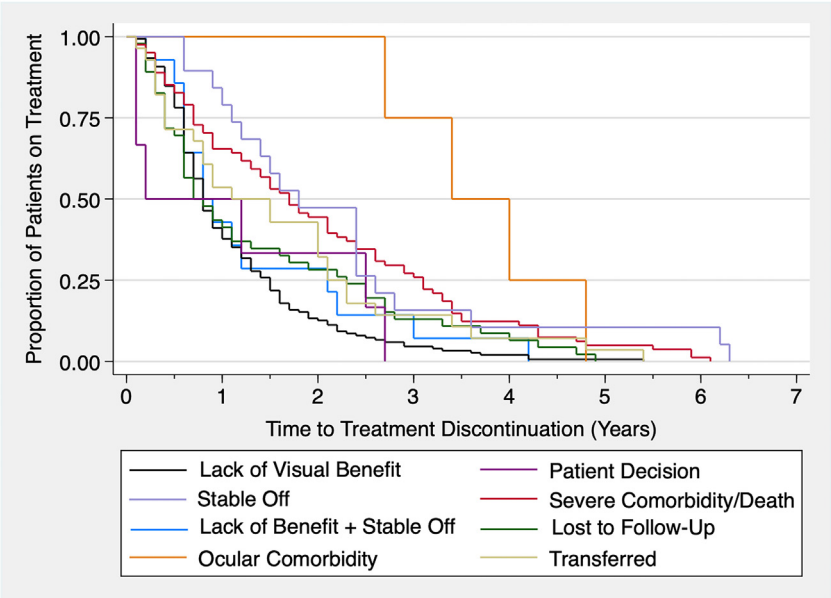


**Fig. 1—Kaplan–Meier survival curves for time to treatment discontinuation by reason for discontinuation.**

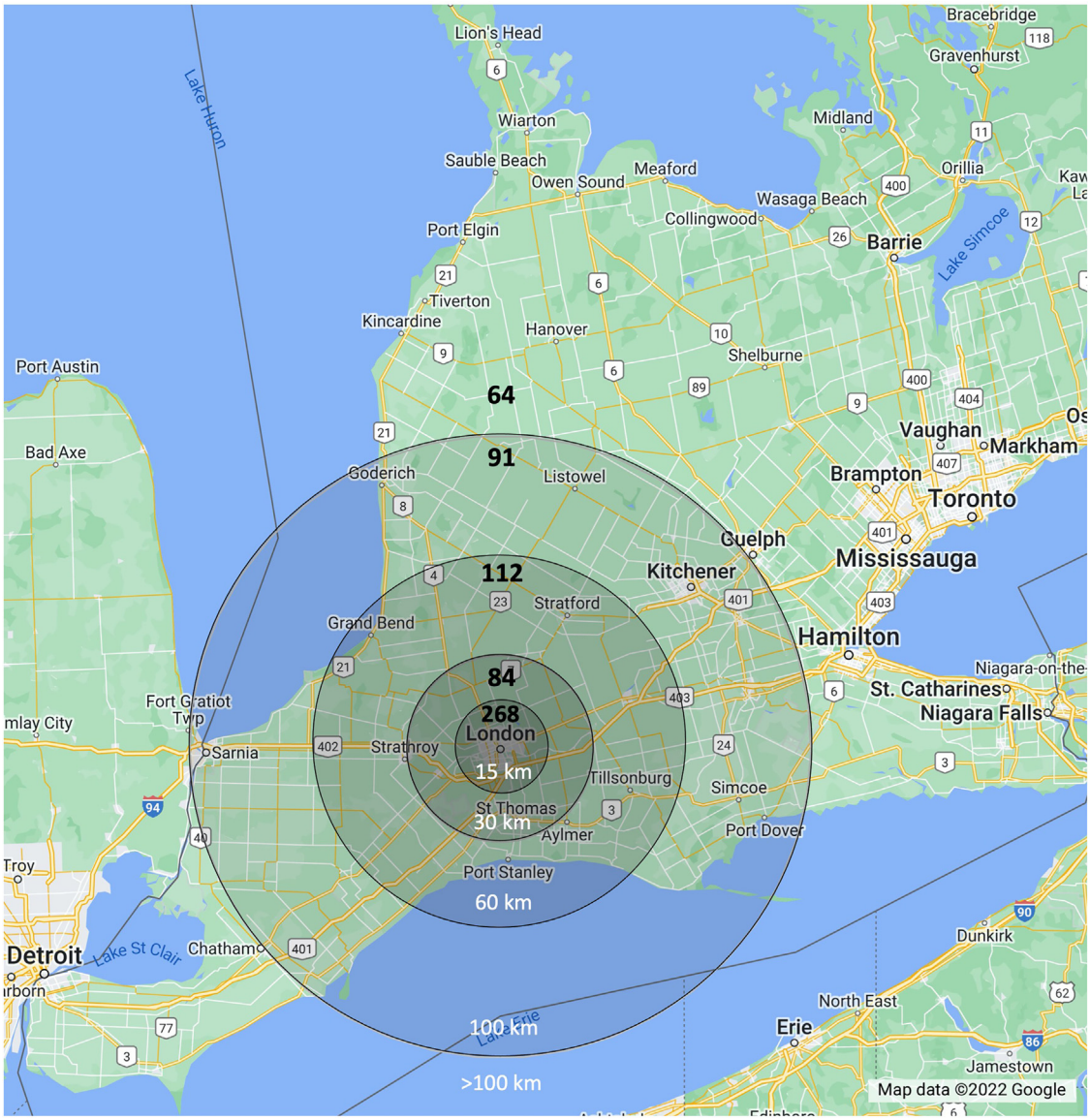


**Fig. 2—Distribution of patient hometown relative to the centre. The numbers of patients living within 15, 30, 60, 100, and >100 km from London, Ontario, are displayed.**

The mean distance from hometown was 35.3 ± 42.4 km. About forty-three percent of patients (268 of 619) live in the same city as the centre, 13.6% (n = 84) live 15 to <30 km away, 18.1% (n = 112) live 30 to <60 km away, 14.7% (n = 91) live 60 to <100 km away, and 10.3% (n = 64) live ≥100 km away. There was no difference between treatment ongoing (34.1 ± 39.7 km) and treatment discontinued (36.1 ± 44.3 km) groups. Distance was greater in the transferred group (92.0 ± 57.3 km) than in those with treatment ongoing ($p < 0.0001$) or discontinued for all other reasons ($p < 0.0001$). There was no significant difference between those lost to follow-up (31.0 ± 38.4 km) and those with treatment ongoing or discontinued.

## Lack of visual benefit

Figure 3 displays the distribution of treatment length and number of injections for 166 eyes discontinued due to lack of visual benefit (n = 152) or lack of visual benefit plus stable off treatment (n = 14). Of these, 59.0% (98 of 166) discontinued within the first year (Table 3). Those with <1 year of treatment received 6.0 ± 1.6 injections over 0.6 ± 0.2 years (approximately 7.5 months), while those with ≥1 year of treatment received 13.4 ± 5.8 injections over 1.9 ± 0.9 years (number of injections, $p < 0.0001$; treatment length, $p < 0.0001$). Those with treatment discontinued within the first year had worse baseline BCVA (<1 year, 1.4 ± 0.5 logMAR vs ≥1 year, 1.1 ± 0.5 logMAR; $p = 0.0002$) and worse final BCVA (1.3 ± 0.4 vs 1.1 ± 0.4

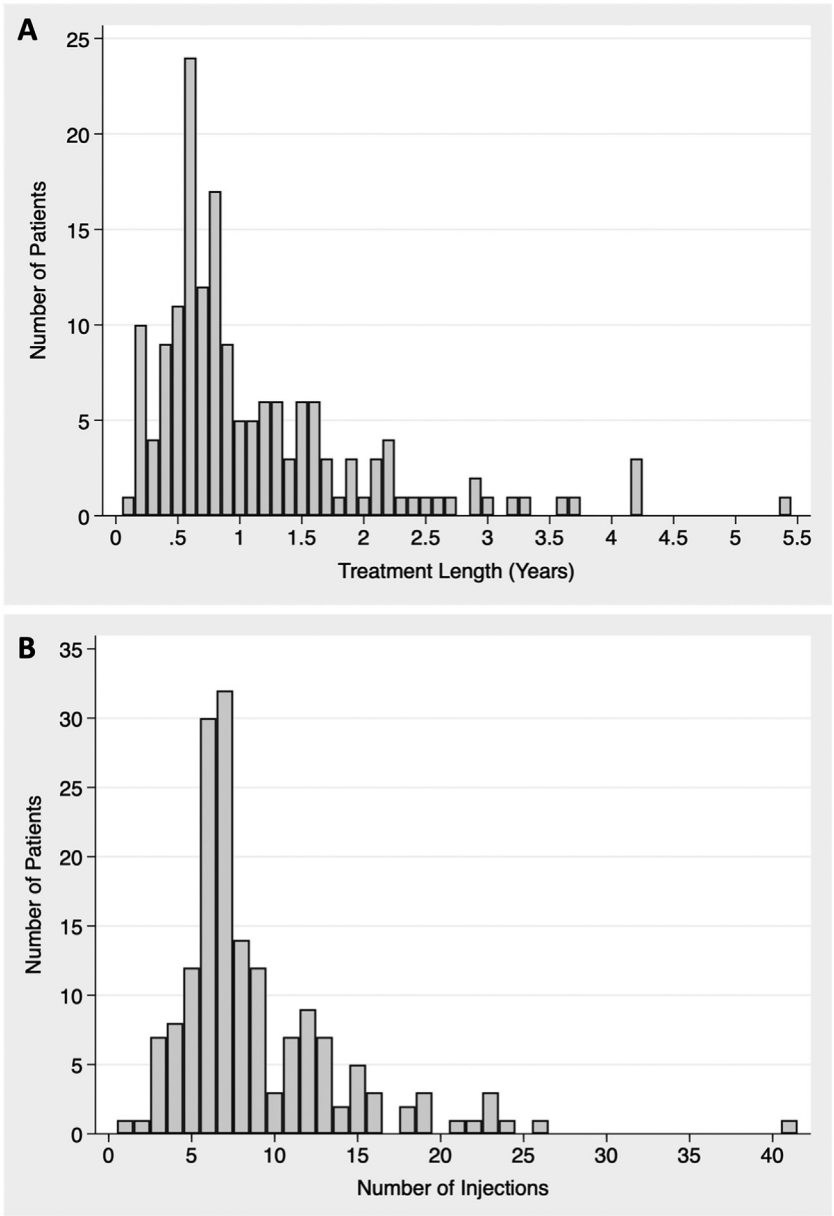


**Fig. 3—Distribution of treatment length (A) and number of injections (B) for eyes with treatment discontinued due to a lack of visual benefit.**

logMAR; $p = 0.0031$). Neither group had a significant improvement in BCVA, but both groups had a reduction in CST ($p < 0.0001$ for <1 year; $p < 0.0001$ for ≥1 year). Sixty-two eyes (37.3%) had atrophy, with 24 in the group with <1 year of treatment and 38 in the group with ≥1 year of treatment.

## Lost to follow-up

Compared with treatment ongoing, those lost to follow-up were older (lost, 82.4 ± 7.4 years vs ongoing, 79.1 ± 8.3 years; $p = 0.0044$), had worse baseline BCVA (0.9 ± 0.5 vs 0.6 ± 0.4 logMAR; $p = 0.0005$), worse final BCVA (0.7 ± 0.4 vs 0.4 ± 0.3 logMAR; $p < 0.0001$), fewer injections (9.6 ± 8.0 vs 20.2 ± 10.9; $p < 0.0001$), and shorter treatment (1.3 ± 1.3 vs 3.3 ± 1.8 years; $p < 0.0001$). Compared with discontinuation due to all other reasons, the lost to follow-up group had better final BCVA (lost, 0.7 ± 0.4 logMAR vs all other discontinued, 0.9 ± 0.6 logMAR; $p = 0.0086$), worse final fellow eye BCVA (0.6 ± 0.5 vs 0.5 ± 0.6 logMAR; $p = 0.0266$), and shorter treatment (1.3 ± 1.3 vs 1.5 ± 1.3 years; $p = 0.0475$).

## Stable off active treatment

Compared with treatment ongoing, those stable off active treatment received fewer injections (stable off, 12.1 ± 4.5 vs ongoing, 20.2 ± 10.9; $p = 0.0011$) over a shorter

**Table 3—Demographic and clinical variables of eyes discontinuing treatment due to lack of visual benefit by treatment length**

| | Treatment length | | |
|---|---|---|---|
| Variable | <1 Year | ≥1 Year | *p* Value |
| No. of eyes (%) | 96 (58.5) | 68 (41.5) | — |
| Baseline age, y | 82.1 ± 7.6 | 79.8 ± 8.5 | 0.1041 |
| Baseline VA, logMAR | 1.4 ± 0.5 | 1.1 ± 0.5 | 0.0002*** |
| Final VA, logMAR | 1.3 ± 0.4 | 1.1 ± 0.4 | 0.0031** |
| Baseline VA fellow eye, logMAR | 0.4 ± 0.4 | 0.6 ± 0.7 | 0.0686 |
| Final VA fellow eye, logMAR | 0.4 ± 0.4 | 0.7 ± 0.8 | 0.1281 |
| Baseline CST, μm | 387.8 ± 137.2 | 369.3 ± 152.3 | 0.2299 |
| Final CST, μm | 249.1 ± 91.5 | 233.5 ± 74.7 | 0.4565 |
| No. of injections | 6.0 ± 1.6 | 13.4 ± 5.8 | <0.0001**** |
| Treatment length, y | 0.6 ± 0.2 | 1.9 ± 0.9 | <0.0001**** |
| Distance from hometown, km | 29.0 ± 43.8 | 30.2 ± 32.8 | 0.2712 |

VA, visual acuity; CST, central subfield thickness.
*Note:* Continuous parameters are reported as mean ± standard deviation. Wilcoxon rank-sum (Mann–Whitney) test was used to analyze variables across groups.
**$p < 0.01$.
***$p < 0.001$.
****$p < 0.0001$.

treatment length (2.3 ± 1.6 vs 3.3 ± 1.8 years; $p = 0.0132$). Compared with discontinuation due to all other reasons, the stable off treatment group was younger (stable off, 72.7 ± 14.7 years vs all other discontinued, 82.1 ± 7.7 years; $p = 0.0055$), had better baseline BCVA (0.6 ± 0.6 vs 1.0 ± 0.5 logMAR; $p = 0.0018$), better final BCVA (0.4 ± 0.6 vs 0.9 ± 0.5 logMAR; $p < 0.0001$), more injections (12.1 ± 4.5 vs 10.5 ± 7.4; $p = 0.0437$), and longer treatment (2.3 ± 1.6 vs 1.4 ± 1.3 years; $p = 0.0034$).

### Effects of the COVID-19 pandemic

Discontinuation was directly attributed to the COVID-19 pandemic for 17 eyes (4.7%). One patient receiving bilateral injections elected to suspend treatment and was found to have stable disease when he returned for care 6 months later. Another patient experienced significant disease progression on return to care 9 months later, and treatment was eventually discontinued due to a lack of visual benefit. One patient was confirmed to have passed away from COVID-19, and 1 patient stopped treatment after having a COVID-related stroke. Additionally, of 51 eyes lost to follow-up over 7.5 years, 12 eyes (23.5%) received their last injection between December 2019 and February 2020. These patients did not return to care again during the study period.

## Discussion

This study is the first to characterize reasons for anti-VEGF discontinuation within a large Canadian population of nAMD patients. Furthermore, this data set captures discontinuation patterns before and during the COVID-19 pandemic. More than half of patients (58%) discontinued treatment during the 7.5-year study period. Reported discontinuation rates vary widely between 20% and 70%, with most estimates ranging between 40% and 50%.[2–4,14,15] Treatment was discontinued within the first year in 49% of patients, similar to previous studies finding discontinuation in half of patients within the first year.[14,15] Visual acuity was at least maintained in all subgroups and improved in the following subgroups: stable off active treatment, severe comorbidity or death, lost to follow-up, and transferred.

The most common reason for discontinuation was a lack of visual benefit. Treatment was discontinued within the first 12 months of therapy in 59%. On average, this occurred at 7.5 months, representing a trial of therapy that was stopped due to no improvement in vision. Those receiving treatment for at least 1 year had better baseline and final visual acuities than those with <1 year of treatment. This may reflect a tendency toward a longer trial of therapy in patients with better baseline visual acuity to maintain this level of vision. Although there was no improvement in visual acuity from baseline, CST did show definite improvement with treatment, suggesting that the drugs were effective at obtaining control. These findings reflect the challenges of predicting which patients will have a visual benefit at baseline and highlight the critical need for predictive biomarkers to guide treatment.[16,17]

The next most common reason for discontinuation was severe comorbidity or death, followed by lost to follow-up. This order of lack of visual benefit as the most common reason and severe comorbidity or death as the second most common reason was maintained in most years. However, 2020 and 2021 were exceptions. As opposed to most years, in which lack of visual benefit was the most common reason for discontinuation, severe comorbidity or death was the top cause for discontinuation in 2021, accounting for one-third of discontinuations that year. Furthermore, 2021 accounted for 30% of discontinuations due to severe comorbidity or death during the 7.5 years. These findings may represent effects of the pandemic not readily apparent from patient charts.

In 2020, lost to follow-up was the second most common reason for discontinuation, as opposed to most years, when severe comorbidity or death was the second most common reason. During 2020, 83% of those lost to follow-up received their last injection in January or February, missing their next scheduled visit from March to May 2020. This corresponds to the onset of pandemic restrictions in Canada. Although there was a relative increase in lost to follow-up during this time, the absolute number of 12 eyes lost to follow-up in 2020 is small considering that a total of 352 eyes received injections that year. Because anti-VEGF injections were considered an essential service, the centre was able to continue providing care.[18] However, COVID-19 created unrest, which may have resulted in a hesitancy to attend hospital-based appointments.[19]

Lost to follow-up rates vary in the literature in part due to multiple possible definitions.[4] Our lost to follow-up rate of 16.5% is lower than those in studies with similar definitions, with reported rates of 22% and 51% in 4-year studies and 57% in a 5-year study.[20–22] Similar to previous studies, those lost to follow-up were older and had poorer baseline

visual acuity.[20,22] Dissatisfactions with vision, treatment burden, travel distance, and treatment unaffordability have been reported by patients to contribute to loss to follow-up.[7,21,22] As expected, discontinuation occurred most commonly in 2 groups: among patients on short treatment intervals (4–5 weeks), perhaps reflecting the burden of frequent injections, and among those on longer intervals (≥12 weeks), making the continued benefits of injections less apparent to patients.[23] Compared with discontinuation due to all other reasons, those lost to follow-up had a better BCVA in the treated eye and a worse BCVA in the fellow eye at the time of their last injection. However, the magnitudes of these differences were small and likely not clinically significant. One previous study has found higher lost to follow-up rates in patients with worse BCVA in the treated or fellow eye at the time of the last injection.[20]. However, other studies have not found this to be an important factor.[24,25]

Setting appropriate expectations for treatment duration and outcomes, emphasizing the importance of adherence, and calling patients who have missed appointments are strategies that may improve adherence.[26] Universal insurance coverage also may decrease lost to follow-up rates.[21,27,28] Anti-VEGF injections are covered by universal health insurance in Ontario for patients over the age of 65. Because 96% of the study population is over the age of 65, this may account for the reduced lost to follow-up rate observed. Contrary to previous studies, distance from hometown was not a significant contributor in this study.[20,22] This is notable because the clinic provides care to a large region in southwestern Ontario, with a significant rural population driving to London, Ontario, for treatment. Clinic notes for patients discontinuing treatment did not reflect travel as a concern. Populations living in these neighbouring cities and towns may regularly travel to larger cities for various reasons, including to receive care from other specialists, so perhaps they do not consider travel for injections to be a significant additional burden.

Treatment was discontinued for a small subgroup of patients with stable disease. They had better baseline and final vision than other discontinuation subgroups. They also underwent treatment for a longer period, likely reflecting a cautious approach to stopping treatment given the good level of vision achieved. Because this subgroup was also the youngest, we hypothesize that they may have wished a trial off therapy due to the prolonged nature of treatment. However, further studies would be required to assess whether age is a factor in the decision to discontinue therapy in patients with stable disease. Interestingly, there were no differences in visual acuity between the stable off treatment and treatment ongoing groups. This demonstrates that a subset of patients may be able to stop treatment with no compromise to their vision. However, given the challenge of identifying which patients will fall into this category, only a small number of patients were discontinued with stable disease in our study population. The conservative approach of ongoing treatment will likely continue to be favoured until we can better predict which patients will remain stable off treatment.

A limitation of this study is the small size of some discontinuation subgroups. Furthermore, the multifactorial nature of treatment decisions could not be reflected in the analysis. For example, providers may be more supportive of a patient's decision to stop injections if that patient's disease has been relatively stable. In such cases, patient preference was reported as the reason for discontinuation because treatment would likely have continued otherwise. The retrospective study design is an additional limitation because reasons for discontinuation could only be determined based on previously documented data. Discontinuation decisions made by the physician or patient were clearly documented in the medical record. To ensure accuracy of the lost to follow-up category, however, our hospital medical record was cross-referenced for cases in which the patient did not attend the scheduled follow-up. This was done to determine whether these cases should be categorized as severe comorbidity or death instead of lost to follow-up.

## Conclusions

A high discontinuation rate was found over 7.5 years, with discontinuation frequently occurring within the first year. Most were attributable to disease or treatment factors and nonmodifiable patient factors. Lost to follow-up was found to make only a minor contribution, which may reflect improvements in disease counselling and patient expectations. Visual acuity was maintained or improved across all discontinuation subgroups.

## References

1. Rosenblatt TR, Rayess N, Al-Moujahed A, Khurana RN, Mruthyunjaya P. Discontinuation and loss to follow-up rates in clinical trials of intravitreal anti-vascular endothelial growth factor injections. Graefes Arch Clin Exp Ophthalmol 2022;260:93–100.
2. Vaze A, Fraser-Bell S, Gillies M. Reasons for discontinuation of intravitreal vascular endothelial growth factor inhibitors in neovascular age-related macular degeneration. Retina 2014;34:1774–8.
3. Dhingra N, Upasani D, Ghanchi FD. Patterns of treatment discontinuation in patients receiving anti–vascular endothelial growth factor for neovascular age-related macular degeneration. Indian J Ophthalmol 2022;70:2065–70.
4. Okada M, Mitchell P, Finger RP, et al. Nonadherence or nonpersistence to intravitreal injection therapy for neovascular age-related macular degeneration. Ophthalmology 2021;128:234–47.
5. Sobolewska B, Sabsabi M, Ziemssen F. Importance of treatment duration: unmasking barriers and discovering the reasons for undertreatment of anti-VEGF agents in neovascular age-related macular degeneration. Clin Ophthalmol 2021;15:4317–26.

6. Giocanti-Aurégan A, García-Layana A, Peto T, et al. Drivers of and barriers to adherence to neovascular age-related macular degeneration and diabetic macular edema treatment management plans: a multi-national qualitative study. Patient Prefer Adherence 2022;16:587–604.
7. Gomi F, Toyoda R, Yoon AH, Imai K. Factors of anti−vascular endothelial growth factor therapy withdrawal in patients with neovascular age-related macular degeneration: implications for improving patient adherence. J Clin Med 2021;10:3106.
8. Pur DR, Bassi A, Malvankar-Mehta MS. Impact on caregivers of patients with eye diseases: systematic review and meta-analysis. Can J Ophthalmol 2022;S0008-4182(22) 00121-1.
9. Ehlken C, Ziemssen F, Eter N, et al. Systematic review: nonadherence and non-persistence in intravitreal treatment. Graefes Arch Clin Exp Ophthalmol 2020;258:2077–90.
10. Zhao X, Meng L, Luo M, et al. The influence of delayed treatment due to COVID-19 on patients with neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. Ther Adv Chronic Dis 2021;12:20406223211026388.
11. Montesel A, Gigon A, Giacuzzo C, Mantel I, Eandi CM. Treatment deferral during COVID-19 lockdown: functional and anatomical impact on patients with neovascular age-related macular degeneration. Retina 2022;42:634–42.
12. Okada M, Wong TY, Mitchell P, et al. Defining nonadherence and nonpersistence to anti−vascular endothelial growth factor therapies in neovascular age-related macular degeneration. JAMA Ophthalmol 2021;139:769–76.
13. Lin T, Dans K, Meshi A, et al. Age-related macular degeneration-associated peripapillary choroidal neovascularization in the era of anti-vascular endothelial growth factor. Retina 2019;39:1936–44.
14. Westborg I, Rosso A. Risk factors for discontinuation of treatment for neovascular age-related macular degeneration. Ophthalmic Epidemiol 2018;25:176–82.
15. Lad EM, Hammill BG, Qualls LG, Wang F, Cousins SW, Curtis LH. Anti-VEGF treatment patterns for neovascular age-related macular degeneration among medicare beneficiaries. Am J Ophthalmol 2014;158:537–43 .e2.
16. Ferrara D, Newton EM, Lee AY. Artificial intelligence−based predictions in neovascular age-related macular degeneration. Curr Opin Ophthalmol 2021;32:389–96.
17. Chaudhary V, Matonti F, Zarranz-Ventura J, Stewart MW. Impact of fluid compartments on functional outcomes for patients with neovascular age-related macular degeneration: a systematic literature review. Retina 2022;42:589–606.
18. Canadian Retina Society. CRS position statement on intravitreal injection treatments 2020. Ottawa: CRS. https://crsscr.ca/2020/03/canadian-retina-society-crs-position-statement-on-intravitreal-injections-and-the-management-of-retinal-diseases-during-the-covid-19-crisis/. Accessed: March 19, 2020.
19. Liu S, Ng JKY, Moon EH, et al. Impact of COVID-19-associated anxiety on the adherence to intravitreal injection in patients with macular diseases a year after the initial outbreak. Ophthalmol Eye Dis 2022;14:25158414211070880.
20. Obeid A, Gao X, Ali FS, et al. Loss to follow-up among patients with neovascular age-related macular degeneration who received intravitreal anti−vascular endothelial growth factor injections. JAMA Ophthalmol 2018;136:1251–9.
21. Kelkar A, Webers C, Shetty R, et al. Factors affecting compliance to intravitreal anti−vascular endothelial growth factor therapy in Indian patients with retinal vein occlusion, age-related macular degeneration, and diabetic macular edema. Indian *J Ophthalmol* 2020;68:2143–7.
22. Boulanger-Scemama E, Querques G, About F, et al. Ranibizumab for exudative age-related macular degeneration: a five year study of adherence to follow-up in a real-life setting. J Fr Ophtalmol 2015;38:620–7.
23. Bakri SJ, Karcher H, Andersen S, Souied EH. Anti−vascular endothelial growth factor treatment discontinuation and interval in neovascular age-related macular degeneration in the United States. Am J Ophthalmol 2022;242:189–96.
24. Droege KM, Muether PS, Hermann MM, et al. Adherence to ranibizumab treatment for neovascular age-related macular degeneration in real life. Graefes Arch Clin Exp Ophthalmol 2013;251:1281–4.
25. Angermann R, Franchi A, Stöckl V, et al. Intravitreal aflibercept therapy and treatment outcomes of eyes with neovascular age-related macular degeneration in a real-life setting: a five-year follow-up investigation. Ophthalmol Ther 2022;11:559–71.
26. McKinney S. Easing the anti-VEGF treatment burden. Rev Ophthalmol 2020.
27. Rozon J-P, Hébert M, Laverdière C, et al. Delayed follow-up in patients with neovascular age-related macular degeneration treated under universal health coverage: risk factors and visual outcomes. Retina 2022;42:1693–701.
28. Narayanan R, Sengupta S. Insurance coverage for intravitreal injections in India—the road ahead. Indian J Ophthalmol 2021;69:1027–8.


## Footnotes and Disclosure

We thank Isabella Randall for her contributions to the administration of this study.

Tom G. Sheidow discloses that he is an investigator for Novartis, Bayer, Roche, Apellis, and Teva. All other authors have no conflicts of interest to report.

A subset of this study was funded by Novartis Pharmaceuticals Canada.

The data that support the findings of this study are available from the corresponding author on request.

From the From the Ivey Eye Institute, St. Joseph's Health Care, London, ON.

Originally received Sep. 22, 2022. Final revision Jan. 25, 2023. Accepted Feb. 15, 2023.

Correspondence to: Amy Basilious, MD, Ivey Eye Institute, St. Joseph's Health Care, 268 Grosvenor Street, London, ON N6A 4V2, Canada; amybasilious@gmail.com.