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ABSTRACT

Purpose To explore the factors and frequency of interruptions in intravitreal treatment for patients with neovascular age-related macular degeneration (AMD) and to evaluate the demographic and clinical factors linked to the reasons for discontinuation.

Methods In this multicentre study, patients who began anti-vascular endothelial growth factor (VEGF) treatment between January 2019 and December 2021 for treatment-naïve neovascular exudative AMD were retrospectively analysed. The overall incidence of treatment discontinuation, along with the rates for each specific cause, was calculated. The probability of each cause of discontinuation over time from the start of treatment, as well as the risk factors associated with each case, was also determined.

Results 655 individuals (28.5%) discontinued intravitreal anti-VEGF therapy. Among the five main categories of causes for discontinuation (patient's decision against clinician's advice, continuation of therapy at another clinic, clinical decision, systemic diseases or death), clinical decision emerged as the most common reason for interruption. The qualitative evaluation of the Kaplan–Meier curves suggests a higher frequency of the clinical decision as a cause of discontinuation within the initial 2 years of treatment. Worse visual acuity increased the risk of discontinuation due to clinical decisions. Younger patients were more likely to stop anti-VEGF therapy by choice. Better visual acuity and longer distance from the clinic increased the likelihood of patients continuing treatment elsewhere.

Conclusions The discontinuation of anti-VEGF treatment is common among individuals with neovascular AMD. Causes of discontinuation include not only clinician decisions but also those related to the patient's health and personal choices.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neovascular age-related macular degeneration (AMD) requires regular and timely intravitreal injections of anti-vascular endothelial growth factor (VEGF) for effective management. However, discontinuation of this treatment is common, leading to discrepancies in outcomes between clinical trials and real-world scenarios.

WHAT THIS STUDY ADDS

⇒ In this multi-centre study, which evaluated data from 2302 patients, 655 individuals (28.5%) discontinued intravitreal anti-VEGF therapy. The most frequent reason for discontinuation was the clinical decision, while other common causes included the patient's decision. Demographic and clinical factors were significant determinants of the reasons for discontinuation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Understanding the reasons behind treatment interruption is crucial as it may lead to improved treatment adherence.

INTRODUCTION

Neovascular exudative age-related macular degeneration (AMD) is a major cause of vision impairment in people aged 50 years and older.[1–3]

The introduction of intravitreal anti-vascular endothelial growth factor (VEGF) therapy has significantly improved outcomes for patients with exudative neovascular AMD. Pivotal clinical trials (ie, the ANCHOR and MARINA trials) evaluated the use of ranibizumab in these patients and demonstrated its effectiveness, with many patients showing improved visual acuity at 12 and 24 months.[4–6] These initial findings marked a critical moment in the treatment of neovascular exudative AMD, demonstrating the effectiveness of anti-VEGF therapy.

However, real-world studies based on chart reviews, electronic medical records or claims analyses have reported less favourable visual outcomes. The reasons for the discrepancies between real-world neovascular AMD studies and randomised controlled trials (RCTs) are unclear, but possible factors include undertreatment.[7–20] A common reason for undertreatment is treatment discontinuation.

In the current study, we examined the factors and frequency of suspension of intravitreal treatment

in AMD patients within a large cohort (2302 individuals) who began treatment between January 2019 and December 2021 for treatment-naïve neovascular exudative AMD at three referral centres in Italy. More importantly, we investigated the demographic and clinical factors associated with the reasons behind discontinuation.

METHODS

Study population

The institutional review board at the University of Turin was notified about this retrospective cohort study (protocol number 0042011) that adhered to the 1964 Helsinki declaration and its later amendments. Patients who participated gave their informed consent for the retrospective use of their data. The data analysis was conducted between January 2024 and June 2024.

Consecutive patients diagnosed with treatment-naïve exudative neovascular AMD between January 2019 and December 2021 were identified from the electronic medical record databases of three medical retina practices: Città della Salute e della Scienza Hospital (Turin, Italy), San Raffaele Scientific Institute (Milan, Italy) and Policlinic of Bari (Bari, Italy). The eligibility criteria for inclusion in the study were as follows: (i) treatment with at least a loading dose of 3 monthly intravitreal injections of anti-VEGF therapy and (ii) a minimum of 2 years of follow-up after the initiation of treatment. Patients with COVID-19 infection resulting in death or severe systemic complications leading to treatment discontinuation were excluded from the analysis. Including these cases could have created an imbalance in the reasons for discontinuation across the years examined. While the deadline to include patients starting intravitreal anti-VEGF therapy was 31 December 2021, data collection continued for at least 2 more years beyond this date to account for any therapy interruptions that might have occurred.

Interruption of treatment and its underlying causes

As previously mentioned, data on whether patients discontinued anti-VEGF therapy were collected over a minimum of 2 years following the initiation of treatment and, in any case, up until the end of the analysis. Patients were considered to have definitively discontinued therapy if there were no anti-VEGF therapy records at the treatment centre for at least 6 months after their last injection. Said differently, to be included in the study cohort of patients with treatment discontinuation, patients needed to have no treatment records up to the end of the analysis, with a minimum 6 month interruption. A 6 month minimum period for treatment interruption has been previously suggested to consider treatment discontinuation,[21] and the latter also based on the assumption that interruptions longer than 6 months can lead to permanent visual acuity loss, even if the treatment is later resumed.[22–24] This assumption heightens our interest in understanding the causes of treatment interruptions.

Age, gender, the date of anti-VEGF therapy initiation, therapy interruption dates, visual acuity at baseline and at the time of discontinuation, distance of the patients' homes from the clinic (based on the patient's residence) and the stated reasons for those interruptions were collected. If both eyes were receiving anti-VEGF treatment, only the first eye treated within 3 years was included in the analysis, while the status of the other eye was considered among the analysed criteria. The reasons for anti-VEGF interruptions were obtained from a standardised checklist completed by the treating clinicians for all patients. Then, they entered the database as part of their termination report. If the cause of the interruption was not readily identifiable (ie, regardless of the outcome considered), the treating physician was allowed to contact the patient by phone. This was done whenever the physician had doubts about the cause of the interruption.

We categorised the reasons for therapy interruptions into five groups, and table 1 provides a complete list and description of each reason.

Statistical analysis

Descriptive statistics included frequencies and proportions for categorical variables, median, first and third quartiles for continuous not normally distributed variables, otherwise the mean±SD. Normality was tested by Jarque–Bera. The X^2 test assessed the statistical significance in proportional differences, and the Kruskal–Wallis and Mann–Whitney non-parametric tests

Table 1 Reasons for treatment discontinuation

Categories	Definition
Clinical decision (n=371)	The treating clinician decided to discontinue treatment.
No signs of exudation (n=197)	The patient received treatment with a PRN or T&E dosing regimen, and discontinuation occurred because of the absence of exudation.
Poor response or non-response (n=173)	Despite treatment, the treating clinician deemed the patient's response as poor or absent, leading to the decision to discontinue treatment.
Development of ocular complications (n=1)	Due to the occurrence of ocular complications possibly associated with the treatment, the treating clinician chose to stop the treatment. These complications included ocular inflammation, endophthalmitis and retinal detachment.
Systemic disease preventing the patient from attending treatment (n=26)	The patient was unable to continue treatment due to a disease that prevented them from attending. This condition may have restricted the patient's mobility at home or, alternatively, increased their hospital visits, thus preventing them from attending the ophthalmology clinic as well.
Cardiovascular disease (n=5)	The disease causing the discontinuation of treatment involved the cardiovascular system, including coronary artery disease, heart failure, arrhythmias, peripheral artery disease and uncontrolled hypertension.
Orthopaedic disease (n=10)	The disease causing the discontinuation of treatment involved the musculoskeletal system, including osteoarthritis, fractures and ligament injuries.
Oncologic disease (n=4)	The disease causing the discontinuation of treatment was cancer.
Pneumological disease (n=0)	The disease causing the discontinuation of treatment involved the respiratory system, including chronic obstructive pulmonary disease and pneumonia.
Neurologic disease (n=3)	The disease causing the discontinuation of treatment involved the neurologic system, including stroke, Parkinson's disease, dementia and peripheral neuropathy.
Others (n=4)	The clinician could not attribute the inability to attend to any of the aforementioned reasons.
Death (n=86)	The discontinuation of treatment was due to the patient's death.
Patient's choice to cease anti-VEGF therapy (n=68)	Despite the clinician's recommendation to continue anti-VEGF treatment, the patient opted to discontinue therapy due to poor motivation or a series of comorbidities, without a specific identifiable reason preventing attendance.
Patient's decision to continue treatment at another clinic (n=104)	The patient opted to transfer to another clinic to continue anti-VEGF therapy.

n, number of patients; PRN, pro re nata; T&E, treat and extend; VEGF, vascular endothelial growth factor.

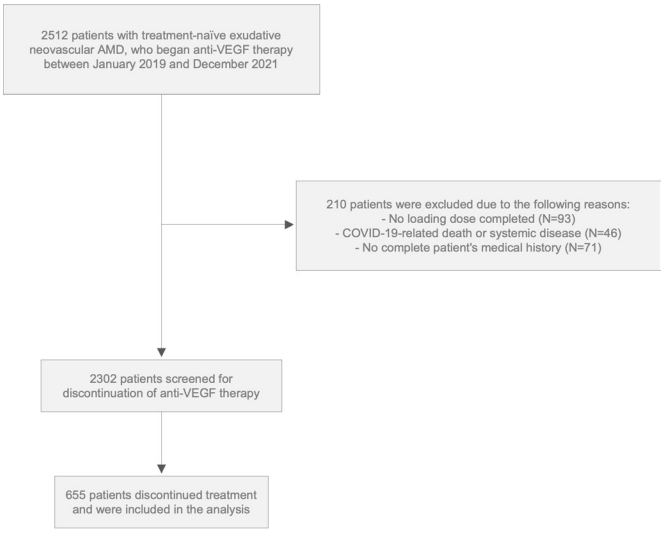

Figure 1 Flowchart of patients with neovascular age-related macular degeneration included in the final analysis.

were employed to compare groups for continuous variables. Indeed, the Wilcoxon sum rank test was used to test differences in paired samples. The Kaplan–Meier curves were used to estimate probability (SE=SE error) of each reason for therapy interruption compared with all the other reasons over time, starting from the initiation of therapy. Multivariable logistic regression models were conducted to explore the factors linked to specific reasons for therapy discontinuation, and adjusted ORs with their 95% CI were calculated. All statistical tests were two-sided, with the significance level set at $p<0.05$. Analyses were performed using the R software environment for statistical computing (version 4.2).

RESULTS

Study cohort characteristics

A total of 2302 patients with neovascular AMD were screened for therapy interruptions (figure 1). Among them, 655 individuals (28.5%) discontinued intravitreal anti-VEGF therapy for various reasons. The mean age of those who discontinued treatment was 80.6±8.2 years (ranging from 58 to 100 years), and 57.9% were women. All patients were Caucasians.

As previously mentioned, all patients received at least a loading dose of 3 monthly anti-VEGF injections. Overall, the median number of anti-VEGF injections before discontinuation was 6.5±4.0 (ranging from 3 to 24). At baseline and the last follow-up visit before discontinuation, visual acuity (LogMAR) was in median 0.70 (0.30;1.00) (p=0.827). The best-corrected visual acuity (BCVA) values for each group are provided in table 2.

Incidence of treatment discontinuation across different years

The overall percentage of treatment discontinuation was calculated for each year of treatment initiation. The rates were similar across the 3 years: 29% in 2019, 29% in 2020 and 27% in 2021. This consistency in discontinuation rates indicated that the study cohort was homogeneous and suitable for combined analysis.

Furthermore, the incidence was categorised based on each reason for therapy interruption (online supplemental figure 1). Clinical decision emerged as the most common reason for interruption across 3 years of therapy initiation, while systemic disease was the least common reason.

Probability of each reason for therapy interruption over time

Kaplan–Meier curves were used to illustrate the likelihood of each cause to all other causes for therapy interruption over time, starting from the initiation of therapy to the last follow-up (figure 2).

The Kaplan–Meier curve regarding clinician decision indicated a steep slope in the initial segment (ie, the first 24 months), followed by a flatter slope in the second part of the curve, implying a higher frequency of this cause within the initial 2 years of treatment. Conversely, other curves representing alternative reasons for discontinuation exhibited a consistent decline, suggesting a comparable likelihood of encountering these causes throughout the observed period. At 12 months, 43.4% (SE=0.022) of the discontinuations were due to a clinical decision. At 24 months, this proportion increased to 68.1% (SE=0.240).

At 36 months, it reached 85.6% (SE=0.023), and at ≥48 months, it was 94.0% (SE=0.020). This showed that clinical decisions become a more prevalent reason for discontinuing therapy.

Study cohort's characteristics based on the reason for discontinuation

Table 2 presents the clinical and demographic characteristics of the study cohort categorised by the reason for discontinuation.

Multivariable logistic regression models were used to explore factors influencing discontinuation for each cause (table 3). Variables in each model were selected based on the analyses in table 1 and clinical considerations. A worse BCVA at the time of interruption was significantly associated with discontinuation due to clinical decision interruption, with an OR of 2.96. The CI (1.95 to 4.64) and a p value of <0.001 underscored the strength and significance of this association.

Patients aged 80 years or younger had 66% lower odds of death compared with those older than 80 years (OR=0.34; 95% CI=0.20 to 0.56; p<0.001). Additionally, males had more than twice the odds of death compared with females (OR=2.22; 95% CI=1.39 to 3.57; p=0.001).

The OR of 4.59 suggested that individuals aged 80 years or younger have about 4.59 times the odds of choosing to discontinue anti-VEGF treatment against clinical advice compared with those older than 80 years.

Regarding the decision to continue treatment elsewhere, patients residing ≥100 km away from the clinic were 6.42 times more likely (95% CI=3.74 to 11.0, p<0.001) to continue treatment at another clinic compared with those living closer.

Subgroup analysis among patients with treatment discontinuation secondary to clinician decision

173, 197 and one single patient discontinued treatment for poor response or non-response,[25] no signs of exudation in pro re nata (PRN) or treat-and-extend (T&E) therapy and development of ocular complications, respectively (online supplemental table 1, figures 2 and 3). The percentage of patients discontinuing treatment due to different sub-causes was similar at the different time points (online supplemental figure 2).

There were demographic and clinical differences between patients discontinuing treatment due to poor response or non-response vs those with no signs of exudation (online supplemental table 1, figure 3). At the last visit before discontinuation, BCVA was better in patients stopping due to no signs of exudation (median=0.45; LogMAR (0.18–0.90)) compared with those discontinuing due to poor response or non-response (median=1.00; LogMAR (0.90–1.60); p<0.001). The total

Table 2 Demographic and clinical characteristics of the study cohort

	Clinical decision	Death	Patient's choice to cease anti-VEGF therapy	Systemic disease preventing the patient from attending treatment	Patient's decision to continue treatment at another clinic	
	n=*371*	n=*86*	n=*68*	n=*26*	n=*104*	
Eye						
Right eye	204 (55.0%)	51 (59.3%)	33 (48.5%)	10 (38.5%)	60 (57.7%)	0.294
Left eye	167 (45.0%)	35 (40.7%)	35 (51.5%)	16 (61.5%)	44 (42.3%)	
Age (at first injection), years	81.0(76.0; 85.0)	86.0(84.0; 89.0)	79.0(74.0; 81.5)	83.0(77.8; 85.8)	77.0(73.0; 82.0)	<0.001
Age (at last injection), years	81.0(77.0; 86.0)	85.0(80.2; 89.8)	80.0(73.0; 85.2)	85.0(77.8; 88.5)	78.0(73.0; 83.0)	<0.001
Age (at last injection), years						
>80	209 (56.3%)	64 (74.4%)	27 (39.7%)	18 (69.2%)	43 (41.3%)	<0.001
≤80	162 (43.7%)	22 (25.6%)	41 (60.3%)	8 (30.8%)	61 (58.7%)	
Gender						
Female	224 (60.5%)	36 (42.9%)	40 (58.8%)	14 (56.0%)	65 (63.7%)	0.036
Male	146 (39.5%)	48 (57.1%)	28 (41.2%)	11 (44.0%)	37 (36.3%)	
Fellow eye with neovascular AMD						
No.	285 (76.8%)	63 (73.3%)	49 (72.1%)	18 (69.2%)	89 (85.6%)	0.146
Yes.	86 (23.2%)	23 (26.7%)	19 (27.9%)	8 (30.8%)	15 (14.4%)	
BCVA (baseline), LogMAR	0.70(0.30;1.00)	0.50(0.30;0.70)	0.65(0.40;1.02)	0.50(0.32;0.98)	0.50(0.30;0.90)	0.001
BCVA (visit before interruption), LogMAR	0.80(0.30;1.30)	0.50(0.35;0.70)	0.50(0.27;0.92)	0.50(0.30;0.80)	0.45(0.20;0.83)	<0.001
Total period of treatment, days	296(90.0;527)	206(84.0;480)	214(87.5;454)	434(147;575)	272(118;523)	0.155
Interval between the last two injections, days	56.0(35.0; 86.5)	44.5(32.0;63.0)	41.0(34.8; 64.0)	62.0(45.8; 92.8)	49.0(34.0; 67.2)	0.083
Number of anti-VEGF injections before interruption	5.00(3.0;8.0)	5.00(3.0;8.8)	5.00(3.0;8.0)	6.00(4.3;10.5)	6.00(4.0;9.0)	0.397
Distance between clinic and patient's residence, kilometres	12.0(8.0;41.0)	11.0(8.0;23.3)	11.5(8.0;49.9)	18.5(10.2;62.9)	48.5(11.8;112.0)	<0.001
Distance between clinic and patient's residence, kilometres						
<100	346 (93.3%)	81 (94.2%)	62 (91.2%)	21 (80.8%)	68 (65.4%)	<0.001
≥100	25 (6.74%)	5 (5.81%)	6 (8.82%)	5 (19.2%)	36 (34.6%)	

Data are presented as median(first; third)quartile for quantitative variables and the absolute frequency (percentage) for qualitative variables.
AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; N, number of patients; VEGF, vascular endothelial growth facto.

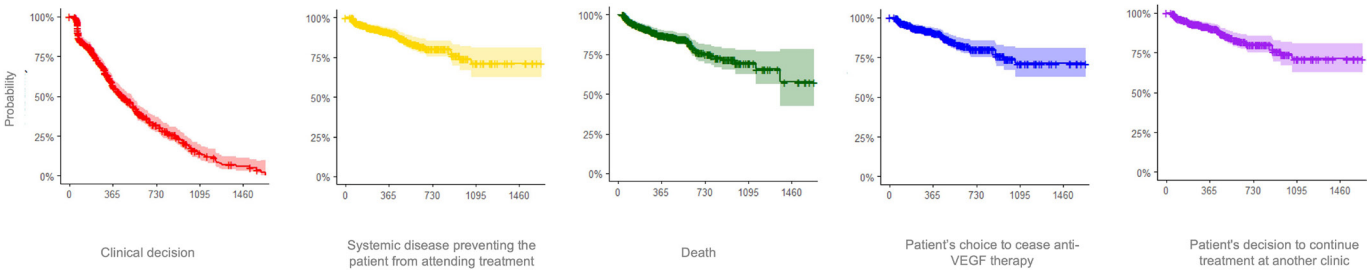

Figure 2 Kaplan–Meier curves showing the probability to interrupt for a cause vs all other causes over time. The horizontal axis (time) represents time in days, and the vertical axis shows the probability of not being interrupted by the cause. The complement of the Kaplan–Meier curve shows a vertical drop in the presence of an event (interrupt for the cause).

treatment duration and the interval between the last two injections were longer for patients who stopped because of no signs of exudation compared with those stopping due to poor response or non-response.

DISCUSSION

In this study, we investigated the reasons for discontinuing anti-VEGF therapy in a large real-world cohort of 2302 consecutive patients with treatment-naïve exudative neovascular AMD. Our findings indicate that therapy discontinuation is relatively common, with 28.5% of patients stopping treatment for any reasons. While clinical decisions remain a primary reason for discontinuation, other factors, such as patient health and personal choices, also contribute to this outcome. More importantly, there are specific risk factors for each cause of discontinuation that can be considered in our clinical practice to help reduce the discontinuation rate. In the present study, the patient's decision to continue treatment at another clinic was considered a reason for discontinuation, even though the patient did not actually stop treatment. This reason was included because the patient effectively interrupted treatment at our centre, and we wanted to understand the factors (eg, residence distance) impacting this specific reason. Without including this reason, the overall incidence of treatment discontinuation would have been 23.9% instead of 28.5%.

In a prior study, Obeid *et al*[26] examined 'loss to follow-up' rates in neovascular AMD patients undergoing anti-VEGF injections, along with associated risk factors. Among 9007 patients treated, 2003 (22.2%) were lost to follow-up, defined as not attending a follow-up visit within 12 months after receiving one or more injections. Factors including older age and greater distance from the clinic were associated with 'loss to follow-up'. However, the latter term does not encompass patients who stop treatment per clinical decision or against advice but still attend regular clinic follow-ups.

A notable finding in our study was that clinical decisions were a common cause of treatment discontinuation (ie, ~16% of the entire cohort). Clinical decisions included no signs of exudation, poor response or non-response and development of ocular complications. While ocular complications were a cause of treatment discontinuation in only one patient (ie, specifically, due to the development of retinal detachment), the absence of signs of exudation in PRN or T&E therapy and poor response/non-response was a common reason for discontinuation. It should be noted that this type of discontinuation does not consider the interruption of clinical visits that were still being conducted.

Patients with neovascular AMD may be treated with various dosing regimens, including T&E (ie, proactive), fixed dosing (monthly or bimonthly) and PRN (ie, as needed). In a recent systematic review and meta-analysis, Nichani and colleagues[27] reported on the efficacy and/or safety outcomes of these dosing regimens. Overall, all these regimens were similar in terms of efficacy and safety. Given the increasing number of patients needing intravitreal injections and the limited capacity of clinics, many patients are treated with PRN or T&E regimens in real-world settings. In our study cohort, approximately 53% (197 out of 371) of patients who discontinued treatment due to a clinical decision did so because of an absence of exudation after a period of treatment. The latter situation occurred due to the absence of exudation relapses in a PRN regimen or after a successful exit strategy in a T&E regimen.[28] This corresponds to an overall incidence of about 8.6% for this reason across the entire study cohort, including those who did not discontinue treatment. Patients who stopped treatment due to the absence of exudation had a median visual acuity of 0.50 LogMAR. This is comparable to patients who discontinued for other reasons but significantly better than those who stopped due to poor or non-response. However, it is important to note that some patients who discontinued for the absence of exudation still had poor visual acuity. This is evident from the wider IQR in visual acuity for this group, indicating some patients had low visual acuity. The absence of exudation is not always a positive clinical outcome, as it can be associated with the development of macular fibrosis and atrophy, which severely impact visual acuity.[29 30]

The remaining 47% of patients who discontinued treatment due to a clinical decision did so because of poor response or non-response (ie, 7.5% of the entire cohort). Poor or non-response to anti-VEGF therapy can result from various clinical factors, including suboptimal dosing, extended dosing intervals, late initiation of treatment and macular complications affecting visual acuity.[25 29] This finding highlights the need to improve treatment strategies for neovascular AMD to reduce discontinuation rates due to poor or non-response. The latter is defined by an absent or unsatisfactory treatment outcome, even in patients with initially good visual acuity.[25] Our results confirm this, as the median visual acuity of patients discontinuing due to poor or non-response is worse compared with those discontinuing for other reasons, although some still have good visual acuity, as indicated by the IQR value.

Another interesting finding in our analysis was that the probability of discontinuing treatment due to a clinical decision was higher within the first 2 years of treatment. This suggests that the absence of exudation after treatment or evidence of poor response or non-response may become apparent early in the treatment course. Finally, based on the reasons mentioned above, it is not surprising that the most significant factor associated with a clinical decision to suspend treatment was poorer visual acuity at the time of interruption.

Table 3 Logistic regression analysis showing predictors associated with each group of cause behind treatment discontinuation

	Clinical decision			Death			Patient's choice to cease anti-VEGF therapy			Systemic disease preventing the patient from attending treatment			Patient's decision to continue treatment at another clinic		
Predictors	ORs	CI	p	ORs	CI	p	ORs	CI	p	ORs	CI	p	ORs	CI	p
Age (≤80 years)	1.23	0.71 to 2.13	0.457	0.34	0.20 to 0.56	**<0.001**	4.59	1.88 to 11.72	**0.001**	0.56	0.22 to 1.27	0.179	0.82	0.39 to 1.75	0.606
BCVA at interruption (LogMAR)	2.96	1.95 to 4.64	**<0.001**				1.61	0.84 to 2.97	0.137				0.20	0.08 to 0.45	**<0.001**
Gender (Male)	0.84	0.60 to 1.17	0.306	2.22	1.39 to 3.57	**0.001**	1.06	0.62 to 1.80	0.822	1.14	0.50 to 2.55	0.751	0.67	0.41 to 1.07	0.099
Age (≤80 years)× BCVA at interruption (LogMAR)	0.73	0.39 to 1.38	0.337				0.35	0.13 to 0.88	**0.027**				3.44	1.25 to 10.20	**0.020**
Distance from clinic (≥100 kilometers)							0.62	0.23 to 1.39	0.285				6.42	3.74 to 11.07	**<0.001**
Observations	624			649			624			649			624		
R^2 Tjur	0.065			0.045			0.022			0.003			0.145		

BCVA, best-corrected visual acuity; p, p-value.

Among the causes of discontinuation not related to a clinical decision, transferring to another clinic to continue treatment was the most common reason. Patients living farther from the treatment centre were more likely to transfer to another clinic, as greater distance poses an increased burden for patients and caregivers.

Increasing age was linked to lower rates of patients discontinuing treatment against clinical advice. This observation could be attributed to two factors. First, older patients may more frequently interrupt treatment due to other health-related reasons, resulting in younger patients being more likely to interrupt treatment by choice. More significantly, younger patients are often more engaged in work and social activities that could be disrupted by ongoing anti-VEGF treatment, making them less motivated to continue the treatment. Unsurprisingly, death was a common reason for treatment discontinuation (the third most common after clinical decisions and transferring to another clinic), with age and male gender being two important risk factors. Previous significant studies have demonstrated that anti-VEGF therapy does not increase the risk of mortality, and the number of injections is also not associated with an increased risk.[31 32] Systemic disease preventing the patient from attending treatment is the least common cause of discontinuation. Orthopaedic disease was a common cause of discontinuation due to systemic disease, which is not surprising given the increased risk of falls and fractures in patients with AMD.[33]

Our study has limitations that should be considered when interpreting the results. The main limitation is that part of the cohort began treatment in 2020, coinciding with the COVID-19 pandemic, which affected access to treatment for neovascular AMD patients.[34 35] This may have led to more patients experiencing poor or non-response to treatment due to delays in starting therapy, potentially increasing treatment discontinuation. Furthermore, the COVID-19 pandemic may have affected patients' overall motivation to attend clinic visits and receive treatments. However, the rate of treatment interruption was similar across patients who began treatment in 3 years analysed, suggesting that while COVID-19 may have impacted visual acuity for patients starting treatment in 2019 or 2020, it did not affect overall discontinuation rates. Notably, we excluded individuals whose treatment was discontinued due to COVID-19-related death or severe complications. Including these cases could have skewed the reasons for discontinuation across the years. Another limitation is that patients were considered to have discontinued treatment if there was no evidence of additional treatment after their last injection, with a minimum follow-up of 6 months. This aligns with literature[21] and recognises that visual acuity can decline within 6 months of stopping therapy,[22 23] making this period clinically significant. Finally, our study was unable to clarify the causes—such as fluid persistence or the development of macular complications—behind treatment interruptions due to poor response or non-response.

In summary, the discontinuation of anti-VEGF treatment is common among individuals with neovascular AMD. Causes of discontinuation include not only clinician decisions but also those related to the patient's health and personal choices.

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Contributors Study concept and design: B, F, U and R. Acquisition, analysis, or interpretation of data: B, F, U, P, I, G, V, P, T, BG, T, G, M, BF, B, R. Drafting of the manuscript: B. Critical revision of the manuscript for important intellectual content:

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Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the institutional review board at the University of Turin that was notified about this retrospective cohort study (Protocol Number 0042011) that adhered to the 1964 Helsinki declaration and its later amendments. Participants gave informed consent to participate in the study before taking part.

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