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# Caregiver Experience Survey of Anti-Vascular Endothelial Growth Factor Treatment for Diabetic Macular Edema and Neovascular Age-Related Macular Degeneration

Francesco Viola<sup>a,b</sup> Gloria C. Chi<sup>c</sup> Nancy M. Holekamp<sup>d</sup>  
Audrey Giocanti-Aurégan<sup>e</sup> Alfredo García-Layana<sup>f</sup> Tunde Peto<sup>g</sup>  
Peter J. Kertes<sup>h</sup> Mirela Mirt<sup>i</sup> Aachal Kotecha<sup>j</sup> Jérémy Lambert<sup>k</sup>  
Hannah B. Lewis<sup>l</sup> Brittany Gentile<sup>m</sup>

<sup>a</sup>Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; <sup>b</sup>Ophthalmological Unit, Fondazione IRCCS Cà Granda – Ospedale Maggiore Policlinico, Milan, Italy; <sup>c</sup>Genentech, Inc., South San Francisco, CA, USA; <sup>d</sup>Pepose Vision Institute Chesterfield, Chesterfield, MO, USA; <sup>e</sup>Ophthalmology Department, Avicenne Hospital, Bobigny, France; <sup>f</sup>Clinica Universidad de Navarra, University of Navarra, Pamplona, Spain; <sup>g</sup>Queen's University Belfast, Belfast, UK; <sup>h</sup>The John and Liz Tory Eye Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; <sup>i</sup>F. Hoffmann-La Roche, Basel, Switzerland; <sup>j</sup>Roche Products Ltd., Welwyn Garden City, UK; <sup>k</sup>Patient Centered Outcomes, ICON plc, Lyon, France; <sup>l</sup>Patient Centered Outcomes, ICON plc, London, UK; <sup>m</sup>Genentech, South San Francisco, CA, USA

## Keywords

Anti-VEGF treatment · Caregiver experience · Diabetic macular edema · Neovascular age-related macular degeneration · Survey

## Abstract

**Introduction:** Diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD) require frequent anti-vascular endothelial growth factor (VEGF) treatment and monitoring visits. We aimed to understand the burden of treatment on caregivers. **Methods:** This multinational, noninterventional study used a cross-sectional survey of adult patients with DME or nAMD treated with anti-VEGF injections in the USA, Canada, France, Italy, Spain, and the UK. The survey assessed caregivers' sociodemographic characteristics, patient relationships,

patients' clinical history and treatment experiences, caregivers' experiences, and the Caregiver Reaction Assessment of caregiving burden. **Results:** Caregivers for patients with DME ( $n = 30$ ) and nAMD ( $n = 95$ ) completed surveys. Mean  $\pm$  standard deviation (SD) age was  $64.0 \pm 13.4$  years, and most were female (71.2%), white (70.4%), married (66.4%), and from Europe (67.2%). Most were caring for their mother/father or partner/spouse (85.6%). Mean  $\pm$  SD length of time as a caregiver was  $9.1 \pm 10.0$  years. Caregivers estimated they provided support for  $4.2 \pm 2.9$  days/week and  $6.0 \pm 7.1$  h/day on average. Nearly half of caregivers (45.6%) reported some impairment in daily activities, and more than two-thirds (70.5%) of working caregivers ( $n = 44$ ) reported work absenteeism due to anti-VEGF treatment/monitoring appointments. At least one treatment barrier was reported by 66.7% and 50.5% of caregivers of patients with DME and nAMD, respectively, which were related to coronavirus

disease 2019- (38.4%), clinic- (18.4%), social-/health- (13.6%), treatment- (10.4%), or financial-related factors (4.8%). Caregiver Reaction Assessment scores indicated mild-to-moderate burden, with higher caregiver schedule disruption scores associated with an increasing number of anti-VEGF treatment/monitoring visits among DME caregivers ( $r = 0.61$ ). **Conclusion:** Caregivers devote substantial time to caregiving, leading to schedule disruptions and absenteeism for some working caregivers. Positive and negative impacts on caregiver mental health were reported.

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## Introduction

Diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD) are associated with vision loss that can lead to blindness if left untreated [1–4]. Patients with these conditions also have reduced functional status and health-related quality of life [5–7].

Anti-vascular endothelial growth factor (anti-VEGF) therapies have been successful in improving and preserving vision and health-related quality of life for patients living with DME or nAMD [8]. However, real-world evidence suggests that the burden of frequent anti-VEGF injections on patients, caregivers, and the healthcare system affects patients' abilities to follow their treatment management plans as recommended [8, 9].

Caregivers have been shown to experience disease-associated burden, which includes having a negative state of mind and disrupted lifestyle when caring for patients with DME or nAMD [9–12]. Treatment-related burden – the need for caregivers to attend appointments – is a notable contributor to the burden on caregivers for both conditions [11, 12], and the inability of caregivers to attend appointments has been found to contribute to patients' nonadherence to treatment in nAMD [11]. In a previous qualitative study, caregivers of patients with DME or nAMD reported that the ability to book an appointment and involvement of caregivers to provide motivation and advice were important drivers of adherence to treatment management plans [9]. It is therefore important to further understand the burden that caregivers, not just patients, experience and to examine the barriers that could hinder their ability to provide optimal care.

The Patient Experience and Preference (PEP) study in DME and nAMD aimed to quantify the current treatment experiences with anti-VEGF injections and barriers to adherence in DME and nAMD from patients' and

caregivers' perspectives in a multinational setting. This manuscript focuses on the experiences of caregivers of patients living with DME or nAMD; the experiences of patients living with DME or nAMD are described separately.

## Materials and Methods

### *Study Procedures and Population*

The PEP study was a multinational, cross-sectional, noninterventional study of patients living with DME or nAMD and their caregivers. Participants were recruited using standardized materials (online suppl. material 1; for all online suppl. material, see <https://doi.org/10.1159/000540390>) via clinical sites in the USA, Canada, France, Italy, Spain, and the UK from January to December 2021. The population recruited was a convenience sample, and reasons for and numbers of participants declining to participate were not collected. Eligible caregivers were 18 years of age or older and were the primary unpaid caregiver of an adult patient with a physician-confirmed diagnosis of DME or nAMD. Caregivers were defined as the main person responsible for the patient's daily care for most of the time that the patient was at home during the past 12 months, the main person who accompanies the patient on anti-VEGF treatment/monitoring visits, or the main person who provides support for activities such as shopping and traveling.

The study complied with local confidentiality regulations and legislation (European Union General Data Protection Regulation, US Health Insurance Portability and Accountability Act, and Canadian Personal Information Protection and Electronic Documents Act). Institutional Review Board/Ethics Committee approval was obtained. Responses were deidentified, and participants were assigned unique identity numbers kept securely and separately from the surveys.

### *Data Collection*

Caregivers completed a survey that was customized for each country and used to collect quantitative data on caregivers' perspectives. The survey was developed following the results of a targeted literature review on DME and nAMD (including treatment) and qualitative research involving interviews with patients with DME and nAMD, clinicians, and caregivers. The methods and findings of the qualitative research are described in depth by Giocanti-Aurégan et al. [9]. The survey was further reviewed by patient advocacy organization

representatives prior to its finalization to ensure it was relevant and well understood.

The survey was available in multiple formats (i.e., paper, online, or via telephone interview), and results were entered into an electronic data capture system. Methods for avoiding multiple/repeat participation, managing nonresponse, and minimizing data errors are described in online supplementary material 1.

The survey comprised (1) questions on the caregiver's sociodemographic characteristics and relationship with the patient, (2) questions about the patient's clinical history and nAMD/DME treatment experience, (3) questions about experiences as a caregiver and impacts of caregiving specific to management of nAMD/DME, and (4) the Caregiver Reaction Assessment to measure general caregiving burden and how the caregiver felt about caregiving. A full copy of the survey is available on request.

#### *Instruments and Scoring*

The Caregiver Reaction Assessment is a self-rated, validated, reliable assessment of general caregiver burden consisting of 24 items representing 5 dimensions of caregiving (schedule disruptions, 5 items; financial problems, 3 items; lack of family support, 5 items; health problems, 4 items; and the impact of caregiving on self-esteem, 7 items) [13, 14]. It is a generic instrument that is not specific to caregiving for any particular health condition. Caregiver Reaction Assessment subscale scores range from 1 to 5, where higher scores represent higher levels of perceived burden, with the exception of the self-esteem subscale, in which higher scores represent higher levels of self-esteem.

#### *Statistical Analysis*

A sample size of 1,600 patients (100 per country per condition in the UK, France, Italy, and Spain, 200 per country per condition in the USA and Canada) was prespecified (online suppl. material 2) with caregiver data for 20–40% of the patient population. Descriptive summary statistics were used to present caregiver survey data. Statistical tests were two-sided (significance taken at 5% [ $p < 0.05$ ]), with 95% confidence intervals used to express uncertainty. Statistical analyses were conducted on caregiver data overall and by patient condition. Scatterplots with Pearson's correlation coefficients depicting the relationship between number of anti-VEGF treatment/monitoring appointments attended by the caregiver and Caregiver Reaction Assessment scores were also developed. Handling of missing data is described in

online supplementary material 2. All programming was conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

## **Results**

### *Description of Participants*

The prespecified recruitment target per country was not fulfilled. Complete data were available for 125 caregivers (30 and 95 caregivers of patients with DME and nAMD, respectively). Of the 125 caregivers, 39 completed the paper version (DME,  $n = 4$ ; nAMD,  $n = 35$ ), 14 completed it by phone (DME,  $n = 4$ ; nAMD,  $n = 10$ ), and 72 completed it online (DME,  $n = 22$ ; nAMD,  $n = 50$ ). The mean  $\pm$  standard deviation age of DME caregivers was younger than that of nAMD caregivers:  $58.0 \pm 15.0$  versus  $66.0 \pm 12.2$  years (Table 1). Overall, most caregivers were female (71.2%), white (70.4%), married (66.4%), and from European countries (67.2%). Most caregivers were either caring for a parent (DME, 33.3%; nAMD, 48.4%) or a partner/spouse (DME, 60.0%; nAMD, 34.7%). Overall, the mean  $\pm$  standard deviation length of time as a caregiver was  $9.1 \pm 10.0$  years. Approximately half (52.0%) of caregivers had college, postgraduate, or professional levels of education. More nAMD than DME caregivers were retired (nAMD, 46.3%; DME, 33.3%), and more DME caregivers were working full time than nAMD caregivers (DME, 40.0%; nAMD, 14.7%). Of all working caregivers ( $n = 44$ ), most were from Spain (29.5%), the UK, or the USA (20.5% each) (online suppl. Table 1). Overall, nearly half (45.6%) of caregivers' annual household incomes were less than USD 59,999/EUR 39,999/GBP 34,999.

### *Treatment Burden*

Caregivers, who reported providing support on a diverse array of tasks, such as household chores, providing transportation to medical appointments, and assisting with administrative tasks, estimated they were providing care  $4.6 \pm 3.0$  days a week,  $7.3 \pm 7.6$  h a day in DME, and  $4.0 \pm 2.9$  days a week,  $5.5 \pm 6.9$  h a day in nAMD. The caregiver-estimated number of days a week spent providing care was mostly consistent among European countries (range,  $3.0 \pm 3.7$  to  $4.7 \pm 2.6$  days/week) but was longer in the USA ( $4.9 \pm 2.8$  days/week) and Canada ( $3.6 \pm 3.3$  days/week). However, the caregivers' estimates of the numbers of hours spent caregiving per day varied considerably between countries, ranging from  $2.3 \pm 1.4$  h a day in Canada to  $12.5 \pm 16.3$  h a day in Italy.

**Table 1.** Sociodemographic characteristics of caregivers

Sociodemographic characteristics, <i>n</i> (%) <sup>a</sup>	DME ( <i>n</i> = 30)	nAMD ( <i>n</i> = 95)	Total ( <i>N</i> = 125)
Age, years			
<i>N</i>	30	93	123
Mean±SD	58.0±15.0	66.0±12.2	64.0±13.4
Q1–Q3	47.0–72.0	57.0–76.0	55.0–75.0
Sex			
Male	7 (23.3)	29 (30.5)	36 (28.8)
Female	23 (76.7)	66 (69.5)	89 (71.2)
Race			
White	25 (83.3)	63 (66.3)	88 (70.4)
Black	2 (6.7)	1 (1.1)	3 (2.4)
Asian	1 (6.7)	0 (0.0)	1 (0.8)
Hispanic or Latino	1 (3.3)	0 (0.0)	1 (0.8)
Multiple race/ethnicities	1 (3.3) <sup>b</sup>	1 (1.1) <sup>c</sup>	2 (1.6) <sup>b,c</sup>
Missing <sup>d</sup>	0 (0.0)	30 (31.6)	30 (24.0)
Education level			
Secondary (high school) or less	14 (46.7)	41 (43.2)	55 (44.0)
Any college <sup>e</sup>	10 (33.3)	31 (32.6)	41 (32.8)
Postgraduate or professional <sup>f</sup>	6 (20.0)	18 (18.9)	24 (19.2)
Missing/other <sup>d</sup>	0 (0.0)	5 (5.3)	5 (4.0)
Country			
Canada	3 (10.0)	10 (10.5)	13 (10.4)
France	0 (0.0)	26 (27.4)	26 (20.8)
Italy	2 (6.7)	3 (3.2)	5 (4.0)
Spain	10 (33.3)	22 (23.2)	32 (25.6)
UK	6 (20.0)	15 (15.8)	21 (16.8)
USA	9 (30.0)	19 (20.0)	28 (22.4)
Working status			
Working full time	12 (40.0)	14 (14.7)	26 (20.8)
Working part time	3 (10.0)	8 (8.4)	11 (8.8)
Self-employed	0 (0.0)	7 (7.4)	7 (5.6)
Retired	10 (33.3)	44 (46.3)	54 (43.2)
Student	1 (3.3)	1 (1.1)	2 (1.6)
Looking after home or family	4 (13.3)	3 (3.2)	7 (5.6)
Unemployed – seeking work	0 (0.0)	4 (4.2)	4 (3.2)
Unable to work due to sickness or disability	0 (0.0)	2 (2.1)	2 (1.6)
Missing/other <sup>d</sup>	0 (0.0)	12 (12.6)	12 (9.6)
Marital status			
Single	6 (20.0)	14 (14.7)	20 (16.0)
Partnership	2 (6.7)	5 (5.3)	7 (5.6)
Married	22 (73.3)	61 (64.2)	83 (66.4)
Divorced/separated	0 (0.0)	11 (11.6)	11 (8.8)
Widowed	0 (0.0)	3 (3.2)	3 (2.4)
Missing/other <sup>d</sup>	0 (0.0)	1 (1.1)	1 (0.8)
Annual household income			
<USD 30,000/EUR 20,000/GBP 15,000	6 (20.0)	21 (22.1)	27 (21.6)
USD 30,000–59,999/EUR 20,000–39,999/GBP 15,000–34,999	7 (23.3)	23 (24.2)	30 (24.0)
USD 60,000–89,999/EUR 40,000–59,999/GBP 35,000–54,999	6 (20.0)	14 (14.7)	20 (16.0)
USD 90,000–119,999/EUR 60,000–79,999/GBP 55,000–74,999	3 (10.0)	4 (4.2)	7 (5.6)
USD 120,000–149,999/EUR 80,000–99,999/GBP 75,000–99,999	2 (6.7)	7 (7.4)	9 (7.2)
≥USD 150,000/EUR 100,000/GBP 100,000	1 (3.3)	3 (3.2)	4 (3.2)
Missing/other <sup>d</sup>	5 (16.7)	23 (24.2)	28 (22.4)

**Table 1** (continued)

Sociodemographic characteristics, <i>n</i> (%) <sup>a</sup>	DME ( <i>n</i> = 30)	nAMD ( <i>n</i> = 95)	Total ( <i>N</i> = 125)
<b>Relationship to patient</b>			
The patient is my spouse/partner	18 (60.0)	33 (34.7)	51 (40.8)
The patient is my mother or father	10 (33.3)	46 (48.4)	56 (44.8)
The patient is my daughter or son	1 (3.3)	0 (0.0)	1 (0.8)
The patient is another family member (e.g., in-law, sibling, grandparent, aunt, uncle, cousin)	1 (3.3)	4 (4.2)	5 (4.0)
The patient is a friend	0 (0.0)	6 (6.3)	6 (4.8)
The patient is an acquaintance or neighbor	0 (0.0)	4 (4.2)	4 (3.2)
Other	0 (0.0)	2 (2.1)	2 (1.6)
<b>Length of time as caregiver, years</b>			
<i>N</i>	28	90	118
Mean±SD	8.1±7.2	9.4±10.7	9.1±10.0
Q1–Q3	3.8–10.0	3.6–10.4	3.6–10.0
Missing	2	5	7

DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration; Q, quartile; SD, standard deviation. <sup>a</sup>Missing data included in calculation of percentages. <sup>b</sup>One caregiver self-identified as white and Asian. <sup>c</sup>One caregiver self-identified as white and Hispanic/Latino. <sup>d</sup>Missing/other including “I prefer not to answer.” <sup>e</sup>Any college includes bachelor’s degree, associate’s degree, vocational training, or some university without degree. <sup>f</sup>Postgraduate or professional includes master’s, doctorate, or professional degree and maybe some bachelor’s degree for France.

However, the small caregiver sample sizes within countries limited the ability to draw robust comparisons.

Nearly half of caregivers (57/125, 45.6%) reported some impairment in their daily activities due to their patient’s treatment with anti-VEGF injections, with most responding that they were affected “a little bit.” Caregivers reported financial impact due to transportation cost (58/118, 49.2%), lost wages (28/110, 25.5%), and out-of-pocket medical expenses (28/115, 24.3%), again with most respondents reporting being impacted “a little bit.” Work absenteeism due to helping with anti-VEGF treatment/monitoring appointments affected 70.5% (31/44) of working caregivers to some extent, with most patients reporting being “somewhat” affected (Table 2).

In general, work impacts were similar at the country level among caregivers. Personal factors were negatively impacted by the anti-VEGF injections/monitoring appointments (including eye examinations), including employment (DME, 33.3%; nAMD, 18.9%), traveling or other leisure activities (DME, 3.3%; nAMD, 13.7%), spending time with family or friends (DME, 3.3%; nAMD, 12.6%), activities of daily living (DME, 13.3%; nAMD, 7.4%), and taking care of someone else (DME, 10.0%; nAMD, 7.4%). Caregivers reported an impact on their mental health, including positive impacts from helping the patient (DME, 43.3%; nAMD, 31.6%) and becoming more thoughtful about their own health (DME,

43.3%; nAMD, 24.2%), as well as negative impacts such as anxiety (DME, 26.7%; nAMD, 20.0%), frustration (DME, 10.0%; nAMD, 5.3%), and depression (DME, 6.7%; nAMD, 1.1%).

#### Treatment Barriers

Over half of caregivers (DME, 66.7%; nAMD, 50.5%) reported one or more barrier that they perceived may affect, or had experienced could affect, the patient’s ability to receive anti-VEGF injections or attend appointments (Table 3). The barriers that caregivers reported at least once were most frequently related to coronavirus disease 2019 (COVID-19; *n* = 48, 38.4%), clinic (*n* = 23, 18.4%), social- and health-related barriers (*n* = 17, 13.6%), treatment (*n* = 13, 10.4%), and financial (*n* = 6, 4.8%) factors. Other caregiver-reported barriers were the patient’s pain and discomfort during/after anti-VEGF injection, difficulty scheduling/rescheduling appointments, the clinic/hospital not allowing caregivers to accompany patients to the appointments, and the caregiver’s availability.

#### Caregiver Reaction Assessment

Overall scores on the Caregiver Reaction Assessment indicated a mild-to-moderate burden on caregivers, with mean subscale scores ranging from 2.0 to 2.5 out of 5 and a low impact on their self-esteem in relation to caregiving,

**Table 2.** Aspects of treatment burden on caregivers

Aspect of treatment burden, <i>n</i> (%) <sup>a</sup>	Disease		Total
	DME	nAMD	
Level/extent of financial impact: due to out-of-pocket medical expenses	<i>n</i> = 29	<i>n</i> = 86	<i>N</i> = 115
Not at all	16 (55.2)	64 (74.4)	80 (69.6)
A little bit	8 (27.6)	10 (11.6)	18 (15.7)
Somewhat	2 (6.9)	5 (5.8)	7 (6.1)
Quite a bit	1 (3.4)	2 (2.3)	3 (2.6)
Missing	2 (6.9)	5 (5.8)	7 (6.1)
Level/extent of financial impact: due to transportation costs	<i>n</i> = 30	<i>n</i> = 88	<i>N</i> = 118
Not at all	13 (43.3)	43 (48.9)	56 (47.5)
A little bit	13 (43.3)	35 (39.8)	48 (40.7)
Somewhat	2 (6.7)	3 (3.4)	5 (4.2)
Quite a bit	1 (3.3)	2 (2.3)	3 (2.5)
A lot	0 (0.0)	2 (2.3)	2 (1.7)
Missing	1 (3.3)	3 (3.4)	4 (3.4)
Level/extent of financial impact: due to lost wages	<i>n</i> = 28	<i>n</i> = 82	<i>N</i> = 110
Not at all	18 (64.3)	59 (72.0)	77 (70.0)
A little bit	3 (10.7)	11 (13.4)	14 (12.7)
Somewhat	2 (7.1)	6 (7.3)	8 (7.3)
Quite a bit	3 (10.7)	3 (3.7)	6 (5.5)
Missing	2 (7.1)	3 (3.7)	5 (4.5)
Level/extent of work absenteeism: due to helping with treatment appointments <sup>b</sup>	<i>n</i> = 15	<i>n</i> = 29	<i>N</i> = 44
Not at all	5 (33.3)	8 (27.6)	13 (29.5)
A little bit	5 (33.3)	8 (27.6)	13 (29.5)
Somewhat	4 (26.7)	10 (34.5)	14 (31.8)
Quite a bit	1 (6.7)	2 (6.9)	3 (6.8)
A lot	0 (0.0)	1 (3.4)	1 (2.3)
Personal factors negatively impacted by injections or examinations	<i>n</i> = 30	<i>n</i> = 95	<i>N</i> = 125
Employment	10 (33.3)	18 (18.9)	28 (22.4)
Taking care of someone else (e.g., child, spouse, parent)	3 (10.0)	7 (7.4)	10 (8.0)
Time with family or friends	1 (3.3)	12 (12.6)	13 (10.4)
Social events	3 (10.0)	6 (6.3)	9 (7.2)
Traveling or other leisure activities	1 (3.3)	13 (13.7)	14 (11.2)
Activities of daily living (e.g., getting dressed, cooking, etc.)	4 (13.3)	7 (7.4)	11 (8.8)
Other	1 (3.3)	2 (2.1)	3 (2.4)
None of my personal factors are impacted by the patient's treatment	13 (43.3)	54 (56.8)	67 (53.6)
Missing	0 (0.0)	3 (3.2)	3 (2.4)
Level/extent of daily activity impairment: due to patient's treatment	<i>n</i> = 30	<i>n</i> = 95	<i>N</i> = 125
Not at all	12 (40.0)	49 (51.6)	61 (48.8)
A little bit	15 (50.0)	28 (29.5)	43 (34.4)
Somewhat	3 (10.0)	10 (10.5)	13 (10.4)
Quite a bit	0 (0.0)	1 (1.1)	1 (0.8)
Missing	0 (0.0)	7 (7.4)	7 (5.6)
Areas of caregiving impact on mental health	<i>n</i> = 30	<i>n</i> = 95	<i>N</i> = 125
It has made me feel anxious (i.e., anxiety)	8 (26.7)	19 (20.0)	27 (21.6)
It has made me feel depressed	2 (6.7)	1 (1.1)	3 (2.4)
It has made me feel frustrated	3 (10.0)	5 (5.3)	8 (6.4)
It has made me feel hopeless	4 (13.3)	1 (1.1)	5 (4.0)
It has made me feel emotional	6 (20.0)	8 (8.4)	14 (11.2)
It has made me feel good to help	13 (43.3)	30 (31.6)	43 (34.4)
It has made me more thoughtful about my own health	13 (43.3)	23 (24.2)	36 (28.8)
It has had no impact on my mental health status	7 (23.3)	41 (43.2)	48 (38.4)
I do not know	0 (0.0)	3 (3.2)	3 (2.4)
Missing	0 (0.0)	2 (2.1)	2 (1.6)

DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration. <sup>a</sup>Missing data included in calculation of percentages. <sup>b</sup>Among employed respondents.

**Table 3.** Caregiver-reported treatment barriers

Treatment barriers, <i>n</i> (%) <sup>a</sup>	DME ( <i>n</i> = 30)	nAMD ( <i>n</i> = 95)	Total ( <i>N</i> = 125)
<b>Treatment-related barriers</b>			
0	24 (80.0)	86 (90.5)	110 (88.0)
1	5 (16.7)	2 (2.1)	7 (5.6)
2	1 (3.3)	2 (2.1)	3 (2.4)
3	0 (0.0)	3 (3.2)	3 (2.4)
Missing	0 (0.0)	2 (2.1)	2 (1.6)
<b>Clinic- and appointment-related barriers</b>			
0	22 (73.3)	78 (82.1)	100 (80.0)
1	5 (16.7)	13 (13.7)	18 (14.4)
2	2 (6.7)	1 (1.1)	3 (2.4)
3	1 (3.3)	1 (1.1)	2 (1.6)
Missing	0 (0.0)	2 (2.1)	2 (1.6)
<b>Financial barriers</b>			
0	26 (86.7)	89 (93.7)	115 (92.0)
1	3 (10.0)	3 (3.2)	6 (4.8)
Missing	1 (3.3)	3 (3.2)	4 (3.2)
<b>Social- and health-related factors</b>			
0	25 (83.3)	81 (85.3)	106 (84.8)
1	4 (13.3)	7 (7.4)	11 (8.8)
2	1 (3.3)	5 (5.3)	6 (4.8)
Missing	0 (0.0)	2 (2.1)	2 (1.6)
<b>COVID-19-related barriers</b>			
0	15 (50.0)	60 (63.2)	75 (60.0)
1	14 (46.7)	30 (31.6)	44 (35.2)
2	1 (3.3)	2 (2.1)	3 (2.4)
3	0 (0.0)	1 (1.1)	1 (0.8)
Missing	0 (0.0)	2 (2.1)	2 (1.6)
<b>All treatment barriers</b>			
0	10 (33.3)	47 (49.5)	57 (45.6)
1	9 (30.0)	30 (31.6)	39 (31.2)
2	4 (13.3)	6 (6.3)	10 (8.0)
3	3 (10.0)	6 (6.3)	9 (7.2)
4	3 (10.0)	2 (2.1)	5 (4.0)
5	0 (0.0)	2 (2.1)	2 (1.6)
6	1 (3.3)	2 (2.1)	3 (2.4)

COVID-19, coronavirus disease 2019; DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration. <sup>a</sup>Missing data included in calculation of percentages.

with mean subscale score of 4.1 out of 5 (Table 4). Subscale scores were consistent across countries. In a visual inspection of scatterplots between the number of anti-VEGF treatment/monitoring appointments and Caregiver Reaction Assessment scores, there was a relationship between having higher scores on the schedule disruption subscale with an increasing number of anti-VEGF treatment/monitoring visits attended by DME caregivers ( $r = 0.61$ ; Fig. 1). The same trend was not evident for nAMD caregivers. However, there was no clear relationship between the number of anti-VEGF

treatment/monitoring visits attended by the caregiver and the financial problems and lack of family support subscales for patients with either DME or nAMD ( $r < 0.50$ ).

## Discussion

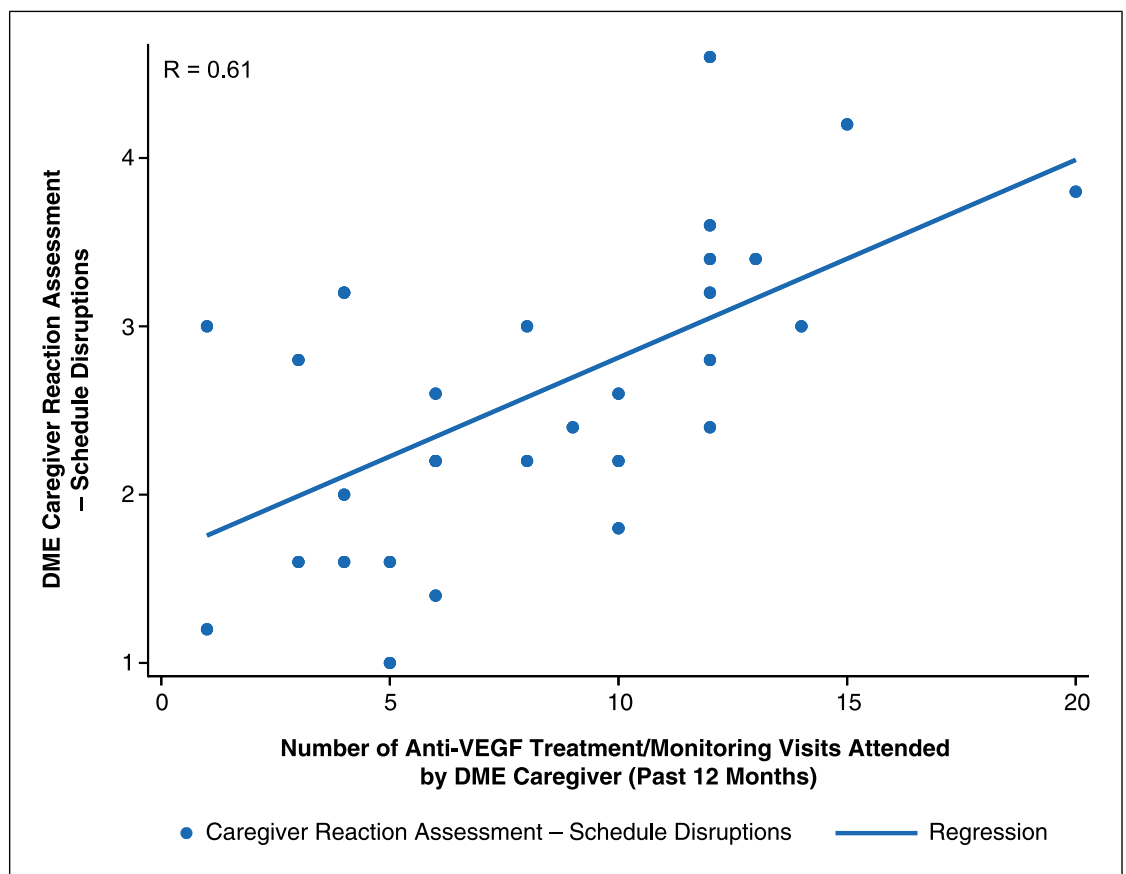
This survey was part of a multinational study that gathered the perspectives of DME and nAMD caregivers on barriers and burden of anti-VEGF treatment.



**Table 4.** Caregiver reaction assessment scores

Caregiver Reaction Assessment scores, mean±SD <sup>a</sup>	DME (n = 30)	nAMD (n = 95)	Total (N = 125)
Schedule disruptions	2.6±0.9	2.4±0.9	2.5±0.9
Financial problems	2.2±0.8	2.1±0.9	2.1±0.9
Lack of family support	2.0±0.7	2.2±0.8	2.1±0.8
Health problems	2.1±0.7	2.0±0.8	2.0±0.8
Impact on self-esteem	4.1±0.7	4.1±0.6	4.1±0.6

DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration; SD, standard deviation. <sup>a</sup>Caregiver Reaction Assessment subscale scores range from 1 to 5. Higher scores represent higher levels of perceived burden with exception of the self-esteem subscale in which higher scores represent higher levels of self-esteem.



**Fig. 1.** Caregiver Reaction Assessment schedule disruption subscale – correlation with anti-VEGF treatment/monitoring visits for caregivers of patients with DME.

Caregivers reported devoting a substantial amount of time to care, which had some impact on their schedules. Attending anti-VEGF treatment/monitoring appointments impaired the daily activities of nearly half of the caregivers, with most respondents reporting “a little bit”

of an impact, and led to some impact on work absenteeism for employed caregivers. Furthermore, most caregivers reported experiencing one or more barrier to the patient’s treatment, consistent with a prior study [15], which may negatively influence ability to follow the

treatment management plan. One of the barriers raised by caregivers was being unable to accompany patients to the appointments, likely related to COVID-19 restrictions, especially as COVID-19 was the most commonly identified barrier. The Caregiver Reaction Assessment indicated a mild-to-moderate burden, and greater schedule disruption was correlated with an increasing number of anti-VEGF treatment/monitoring visits attended by DME caregivers.

Compared with nAMD caregivers, DME caregivers were generally younger, more likely to be working full time, and less likely to be retired. Combined with the slightly longer hours of care per day provided by DME caregivers, more DME caregivers experienced a negative impact of caring on employment, reported barriers to anti-VEGF treatment, and experienced greater schedule disruptions that correlated with number of anti-VEGF treatment/monitoring visits than nAMD caregivers. To our knowledge, this is the first time that these differences between DME and nAMD caregivers have been reported, although we have shown differences in opinions of DME caregivers compared with other groups before; in qualitative interviews, concerns over financial burden and temporary decrease in visual acuity were reported as barriers by a higher percentage of DME caregivers than any other groups of participants [9]. The findings of both of these studies could be artifacts of low sample numbers, but they could also reflect differences in the demands of anti-VEGF treatments and care activities for the two diseases; this warrants additional study.

A literature search for caregiver burden in DME yielded a single Japanese study that factored caregiver productivity loss into a model of the financial burden on caregivers and patients with DME [16]. A cross-sectional study of caregivers in India for people with visual impairment generally found a significant association between caregiver burden and depression, as well as between the degree of the patient's disability and the caregiver's burden [17]. Although this study supports our findings overall, it is unclear whether any of the caregivers were caring for patients with DME specifically. The outcomes of our study expand the understanding of caregiver burden into another retinal disease.

The findings in the present study align with previous research into caregiver burden around nAMD treatment, including our previous qualitative work. In support of our findings of a substantial burden, involving significant time and schedule disruption, previous research has shown that caregiving in DME and nAMD involves helping patients with daily activities, including errands/shopping and booking and attending appointments [9].

Moreover, caregivers' well-being is impacted by feelings of concern and worry for the patient; anxiety, frustration, and depression; and the need to manage the patients' feelings as well as their own, despite positive impacts also being reported [9, 18].

The caregivers' sexes and relationships to the patients in this study are comparable to those previously reported in nAMD [19–21], other eye diseases [17], and chronic conditions [22]. Multiple studies in nAMD have revealed that caregiver attendance at appointments is a notable contributor to caregiver burden [11, 12, 20], even though their presence can positively affect the patient's adherence to treatment [11]. Similarly, Gohil et al. [19] found that caregivers of patients with nAMD had to take time off work, with loss of income, to attend appointments that could take most of the day. Hanemoto et al. [21] reported that nAMD caregivers in Japan spent an average of 236 min per visit (almost 33 h/year) when accompanying patients. Caregiver concerns over the financial burden of treatment and traveling long distances for treatment have also been previously reported in the context of nAMD [20]. Our qualitative research also showed that most patients and caregivers reported negative impacts to their daily routine, both due to anti-VEGF treatment side effects and adjustments to, and difficulties with, daily or planned activities [9].

Our results are aligned with a previous survey study showing a high percentage (77%) of nAMD caregivers reporting barriers to treatment (vs. 50.5% in our study) [9]. However, the main barrier reported by caregivers in the survey study was related to anti-VEGF treatment, consistent with our qualitative research in which the most impactful barriers were related to tolerability and side effects, including pain, discomfort, and irritation [9, 15]. The higher importance placed on COVID-19 and clinic- and appointment-related barriers in our study can be explained by the timing of our study. The Caregiver Reaction Assessment scores indicated a mild-to-moderate burden on caregivers, in line with a previous study of caregivers in nAMD using this measure, which found comparable burden to that of caregivers of patients with atrial fibrillation who had regular thromboprophylaxis monitoring appointments [19].

Overall, previously reported studies and the findings reported here reinforce the impact of regular eye clinic appointments on the caregiver burden and support the need for a reduced anti-VEGF treatment/monitoring visit frequency, as well as time spent waiting at clinics. Our own qualitative research has shown that caregivers identified the ease of booking appointments for the patient and caregiver involvement to be drivers for

following the anti-VEGF treatment management plan, highlighting the importance of caregivers' needs in the delivery of optimal treatment for patients with DME and nAMD [9].

The requirement for regular anti-VEGF treatment/monitoring visits to avoid worsening disease needs to be addressed to reduce the burden of frequent visits on patients and caregivers [3, 9]. New drug delivery methods have been developed that could reduce the frequency of visits without compromising efficacy [23], and disease monitoring of quiescent nAMD in community settings rather than hospitals could be less burdensome for patients and caregivers [24]. In addition, improvements in visual acuity with effective treatments in DME and nAMD have been found to improve caregiver productivity and reduce dependence on the caregiver, thus reducing the burden for caregivers [10, 16].

This study had several strengths. The survey was part of a study across six countries combining qualitative and quantitative approaches to gather the perspectives of patients with nAMD and DME and their caregivers. The quantitative survey was designed using data from previous qualitative interviews, and the survey was reviewed by patient advocacy organization representatives to ensure its relevance and clarity. Furthermore, the survey was available in multiple formats to optimize participation. A validated Caregiver Reaction Assessment was also used.

The study also had limitations. Due to recruitment limitations during the COVID-19 pandemic period, sample sizes were too low to draw country-specific conclusions; for instance, only five caregivers were recruited from Italy. COVID-19 also limited caregiver access to the clinic for appointments, as many were not permitted to accompany patients. There was limited diversity in caregiver ethnicity/race, despite efforts to include a diverse range of sites. As race can affect healthcare access and utilization [25, 26], a more racially diverse population could have provided more valuable sociodemographic insights in this study. The multinational design enabled findings that are primarily generalizable to patients across North America and Europe; however, of the small sample of DME caregivers, 50% were from the UK or the USA. Access to and quality of healthcare between regions differ [27, 28], as does the level of governmental support afforded to working caregivers [29]. The low recruitment of caregivers from across different European countries may therefore limit the conclusions that can be drawn in these settings. The DME caregiver sample size was small because fewer DME than nAMD patients had caregivers. It must also be noted that responses to the

survey questions may be subject to recall and information bias. Lastly, this study primarily assessed caregiver burden in relation to nAMD/DME management specifically. It did not assess burden associated with additional health conditions these patients may be experiencing, which could be a topic of future research.

## Conclusions

Caregiver burden included accompanying patients for frequent anti-VEGF treatment/monitoring visits and spending a substantial amount of time on caregiving. Treatment burden had some impact on caregivers' schedules and daily activities, and caused absenteeism for some working caregivers. Although negative feelings of anxiety, depression, and frustration have been reported, caregivers may also derive some positive impact from taking care of their patients and becoming more mindful of their own health. Most caregivers reported one or more barrier that prevented patients from receiving treatment that included COVID-19-, clinic-, social-, health-, and treatment-related factors. Alleviating the impact of anti-VEGF treatment/monitoring visits with access to more durable regimens with longer treatment intervals may help reduce the impact on patients and caregivers.

## Acknowledgments

We thank the caregivers who took part in the survey. We also would like to thank all participating sites and the associated principal investigators for their support of this study. A full list of the participating sites is available in online supplementary Table 2.

## Statement of Ethics

The study protocol and study materials were reviewed and approved by the local authorities and Institutional Review Boards as follows: Advarra IRB (Aurora, ON, Canada; approved November 20, 2020); Comité de Protection des Personnes Sud-Méditerranée III (reference 2021.02.07 bis\_20.11.18.48450), CNIL Data Protection Authority (reference CNIL 921172\_MR41928 [EudraCT 2020-A02937-32] Roche) (France); Comitato Etico Centrale Fondazione G.B. Bietti IRCCS Lazio (reference N.112/21/FB), Comitato Etico delle Province di Chieti e Pescara (reference MR41928-ITA003), Comitato Etico Milano Area 2 (reference 742\_2021), Comitato Etico Area Vasta Emilia Centro (reference 2028/2021) (Italy); CEIm Grupo Hospitalario Quirónsalud-Catalunya (reference 2021/19-OFT-HUGC), Comitè Ètic de la Investigació, Hospital Universitari de Bellvitge (reference

EPA027/20), Comité de Ética de la Investigación con Medicamentos (CEIm) Área de Salud Valladolid Oeste (reference 21-EO017), CELM de la Comunidad Foral de Navarra (reference 0165/0596 Roche Spain) (Spain); Health Research Authority (HRA) Research Ethics Committees (REC) (references EC Ref: 19/EM/0259 and IRAS ID: 267010) (UK); and Advarra IRB (Aurora, ON, Canada, reference MOD00824561) (USA). Written informed consent was obtained from participants prior to participating in the survey.

## Conflict of Interest Statement

F.V. is a consultant for AbbVie, Bayer, Novartis, and Roche. G.C.C. and B.G. were employees of Genentech, Inc., at the time the study was conducted. N.M.H. has received consulting fees from AGTC, Allergan, Annexon, Apellis, Bayer, Cardinal, Clearside Biomedical, EyePoint, Gemini, Genentech, Inc., Gyroscope, Laboratoires Théa, Nacuity, NGM, Notal Vision, Novartis, Ocuphire, Outlook Therapeutics, Regeneron, and Stealth Biosciences; has been on speakers bureaus for Allergan, Apellis, Genentech, Inc., Regeneron, and Spark; has been contracted for research by Gemini, Genentech, Inc., Gyroscope, and Notal Vision; and has intellectual property/patents with Katalyst Surgical. A.G.-A. is a consultant for AbbVie, Alcon, Bayer, Horus, Laboratoires Théa, Novartis, and Roche. M.M. and A.K. were employees of Roche at the time the study was conducted. J.L. and H.B.L. were employees of ICON at the time the study was conducted.

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## Author Contributions

Study design: G.C.C., M.M., B.G., H.B.L., and J.L.; quantitative analysis: H.B.L. and J.L.; data review and interpretation, critical review of the manuscript, and approval of the final version prior to its submission: F.V., G.C.C., N.M.H., A.G.-A., A.G.-L., T.P., P.J.K., M.M., A.K., J.L., H.B.L., and B.G.

## Data Availability Statement

The datasets obtained and/or analyzed during this study are not publicly available for reasons of patient confidentiality. They are available from the corresponding author (Francesco Viola, Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy; Tel: +39 025 032 0457; Email: francesco.viola@unimi.it) upon reasonable request.

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