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Intravitreal anti-VEGF use in France: a cross-sectional and longitudinal Nationwide observational study

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ABSTRACT.

Purpose: **To describe the sociodemographic, medical and management characteristics of patients using intravitreal (IVT) anti-vascular endothelial growth factors (VEGF) in France.**

Methods: **An observational study was conducted in patients treated with IVT ranibizumab or aflibercept, aged 18 years or older using the French National Health Insurance Databases covering 99% of the French population. Patients currently treated in 2018 were included in a cross-sectional approach to describe treatment history over the previous 6 years. Patients newly treated between 2014 and 2018 were included in a longitudinal approach to describe treatment management during up to 6 years of follow-up. Sociodemographic characteristics and medical history were described in both populations. The analyses were performed at the patient level, as no distinction between the eyes could be made.**

Results: **A total of 224 775 current users of IVT anti-VEGF in 2018 (mean age 78.1 ± 11.3 years, 60% female) and 330 969 new users between 2014 and 2018 (mean age 75.9 ± 12.0 years, 59% female) were included. In both populations cardiovascular comorbidities or risk factors were frequent and the main treatment indications were age-related macular degeneration and diabetic macular oedema. Among current users of IVT anti-VEGF in 2018, the mean number of years receiving a treatment was 2.9 ± 2.0 years, with a mean of 13.7 ± 11.8 dispensations. In the longitudinal approach, a 26% increase in IVT anti-VEGF initiation was observed between 2014 and 2018. For new users, the mean number of years receiving a treatment was 1.6 ± 1.6 and 67% had at least three dispensations within the first three months. A treatment interruption was observed for 83% of new users and occurred on average of 6.1 ± 8.1 months after initiation. The mean number of dispensations was 4.8 ± 2.8 in the first year and 2.2 ± 2.9 in the second year. The mean number of eye monitoring examinations was 6.5 ± 4.7 in the first year and 4.6 ± 4.4 in the second year.**

Conclusion: **This study described the real-world conditions of IVT anti-VEGF dispensing at the entire French population scale. Less frequent dispensations and surveillance examinations were observed than in monthly schemes applied in registration trials for IVT anti-VEGF. These results may indicate a lack of systematic monitoring associated with fewer injections and/or clinicians' preference for more flexible and personalized injection schemes than those originally recommended.**

Key words: aflibercept – age-related macular degeneration – choroidal neovascularization – intravitreal anti-vascular endothelial (anti-VEGF) growth factor – longitudinal study – macular angiogenesis – pharmacoepidemiology – ranibizumab – real-world study

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Introduction

Neovascular age-related macular degeneration (nAMD) is a leading cause of irreversible vision loss among individuals over 50 years of age in industrialized countries (Jager et al. 2008). Its prevalence rises from 0.7% in people aged 65–74 to 8.5% after 84 years (Lambert et al. 2016), and the disease has a growing public health impact due to population ageing (Li et al. 2019). Intravitreal anti-vascular endothelial growth factors (IVT anti-VEGF) have revolutionized the management of the disease (Brown et al. 2006; Rosenfeld et al. 2006). Pegaptanib, the first IVT anti-VEGF approved in Europe in 2006 to treat nAMD, was withdrawn in 2014 after the introduction of other anti-VEGF (i.e. ranibizumab in 2007 and aflibercept in 2012) which demonstrated an improvement in vision (Brown et al. 2006; Rosenfeld et al. 2006; Heier et al. 2012). In 2015, bevacizumab, an anti-VEGF approved in oncology, received a recommendation for IVT use in nAMD in France because of its similar effectiveness (CATT Research Group et al. 2011) and minimized cost compared to other anti-VEGF. Since 2011, ranibizumab and aflibercept have been approved in Europe (and France) for the treatment of diabetic macular oedema (DME), macular oedema secondary to retinal vein occlusion (RVO) and myopic choroidal neovascularization (myopic CNV). In France, IVT

anti-VEGF are fully covered by the health authorities upon presentation of a medical prescription attesting to an indication requiring such a treatment, with no restriction on the number of reimbursed injections. For most IVT-anti VEGF indications, the original summaries of products recommend a loading phase (i.e. one monthly injection for three consecutive months) followed by a flexible maintenance regimen for ranibizumab or for aflibercept via (i) a bimonthly injection, the rest of the first year, and (ii) a flexible maintenance regimen protocol, after the first year. A loading phase of 5 months is recommended for the initial treatment of DME with aflibercept. For myopic CNV, less frequent injections might be sufficient (European Medicine Agency 2009, 2012; Sayanagi et al. 2019). In practice, the wide variability in patient response to IVT anti-VEGF and the clinical burden may lead to the development of alternative injection strategies to reduce the number of injections needed to maintain or improve visual acuity (Fung et al. 2007; Oubraham et al. 2011; Semoun et al. 2017). This study, conducted on almost the entire French population using national medico-administrative databases, aimed to describe the characteristics and management modalities of patients treated with IVT anti-VEGF (i) in a cross-sectional manner among patients currently treated in 2018 benefiting from a 6-year history and (ii) prospectively among patients newly treated between 2014 and 2018, followed up to 6 years. The analyses were performed at the patient level, as no distinction between the eyes could be made.

Materials and Methods

Data source

The French National Health Insurance Databases ("Système National des Données de Santé"–SNDS) were used to identify patients with IVT anti-VEGF dispensations between 01-01-2012 and 12-31-2018. The SNDS contains anonymous and individual data on all reimbursed health expenses for 99% of the French population (i.e. over 66 million inhabitants), including medicines (Anatomical Therapeutic Classification-ATC codes), outpatient medical and nursing care prescribed or performed by healthcare professionals, and out-of-hospital laboratory tests (without results). Medical indications for outpatient reimbursements are not available, but the patient's status for 100% reimbursement for care related to a serious and costly long-term disease (e.g. cardiovascular diseases, diabetes, cancer etc.) is recorded and coded according to International Classification of Diseases, 10th revision-ICD-10, along with the date of the onset of the disease. The SNDS also contains sociodemographic data such as age, sex, area of residence (ZIP code), affiliation to complementary universal health insurance, corresponding to free access to healthcare for people with an annual income <50% of the poverty threshold (attributed to 5.6 million inhabitants under 65 years of age) and deprivation index, corresponding to an index of the participant's area of residence calculated from socio-economic data (Rey et al. 2009). This information is chain-linked via a unique and anonymous individual identifier to the national hospital database, which covers all admissions and discharges from public and private hospitals and contains information about hospitalization stays: admission and discharge dates, ICD-10 coded diagnoses, care and surgical procedures, expensive drugs or medical devices provided. These databases have been fully described elsewhere (Bouillon et al. 2015; Raguideau et al. 2016; Weill et al. 2016; Bezin et al. 2017; Lemaitre et al. 2017; Bouillon et al. 2018).

Study populations and observation periods

Patients aged 18 years or older who received at least one IVT anti-VEGF (i.e. pegaptanib-ATC code S01LA03, ranibizumab-S01LA04, aflibercept-S01LA05, bevacizumab-L01XC07) dispensation between 01-01-2012 and 12-31-2018 were initially identified using the SNDS databases. Intravitreal (IVT) bevacizumab users were not included because this drug is rarely prescribed (e.g. 158 patients treated in 2018) and used only in hospitals in France.

Cross-sectional approach: patients currently treated in 2018

Patients with at least one dispensation of IVT ranibizumab or aflibercept in 2018 (i.e. current users) were included in a cross-sectional approach. The index date was the first IVT anti-VEGF dispensing date recorded in 2018. A 6-year history was available for all current users in 2018.

Longitudinal approach: patients newly treated between 2014 and 2018

Patients with a first dispensation of IVT ranibizumab or aflibercept between 2014 and 2018 (i.e. new users) and having at least one year of follow-up, were included in a longitudinal approach. New use was defined as the absence of any IVT anti-VEGF (i.e. pegaptanib, ranibizumab, aflibercept or bevacizumab) dispensation in the previous two years. The index date was the first IVT anti-VEGF dispensing date recorded between 2014 and 2018. New users were followed up from the index date until one of the following events, whichever came first: end of observation period (12-31-2019), death, lost to follow-up, new episode of IVT anti-VEGF treatment (i.e. occurring ≥2 years after the last dispensation of the previous episode).

Sociodemographic characteristics and medical history

For current and new users of IVT anti-VEGF, sociodemographic characteristics (sex, age, affiliation to complementary universal health insurance, deprivation index) were measured at the index date. History of ischaemic heart disease (including myocardial infarction), arrhythmia or conduction disorders (including non-valvular atrial fibrillation), heart failure, stroke, as well as indicators of chronic smoking, morbid obesity and chronic alcoholism, were measured in the 6 years prior to the index date. The dispensing of antihypertensive, lipid-lowering, antiplatelet, antidiabetic, anticoagulant and antiarrhythmic treatments was measured in the year preceding the index date. The history of ocular hypertension or glaucoma and that of treatments sharing some of the indications of the IVT anti-VEGF (i.e. intravitreal implant, laser photocoagulation, photodynamic therapy) were measured in the year preceding the index date.

For new users of IVT anti-VEGF, the history of eye surgery and eye examinations (i.e. optical coherence tomography – OCT, fluorescein or indocyanine green angiography, dilated

fundus and fundus photography) performed as part of the management of retinal diseases were measured, respectively, in the month and the year preceding the index date. Finally, the history of cancer was recorded in the year preceding the index date. Medical history was identified from the CIM-10 codes recorded at the time of hospitalization or registration for a long-term disease, or from reimbursements for medication or care specific to a disease. The algorithms used to identify medical history in the SNDS are provided in Table S1.

Characteristics related to current use of IVT anti-VEGF in 2018 in the cross-sectional approach

Among patients currently treated with IVT anti-VEGF in 2018, the molecule dispensed and the prescriber's speciality (i.e. ophthalmologist, general or hospital practitioner - the prescriber speciality being unavailable in the context of hospitalization) were described at the index date. In the absence of information directly available in the SNDS, likely and possible indications of IVT anti-VEGF were estimated based on information measured in the two years preceding and following the index date. The algorithms used to estimate treatment indications are provided in Table S1. The duration receiving treatment, the number of dispensations and the molecules dispensed since 2012 were assessed among current users who initiated treatment before 2018.

Characteristics related to new use of IVT anti-VEGF between 2014 and 2018 in the longitudinal approach

Initial dispensing
The first IVT anti-VEGF molecule prescribed and the speciality of the initial prescriber were identified at the index date. Intravitreal (IVT) anti-VEGF indications were estimated in the same way as for current users.

Duration receiving treatment and treatment interruption
The duration receiving IVT anti-VEGF was estimated as the time period between the index date and the last IVT anti-VEGF dispensing date. The number of patients with at least one treatment interruption during the follow-up was evaluated. Treatment interruption was defined as a time period of more than 6 months between two IVT anti-VEGF dispensations or between the last IVT anti-VEGF dispensation and the end of follow-up. The interruption date corresponds to the most recent date in these intervals. The time period between the index date and the first interruption date (if any) was assessed.

Number of dispensing dates and time intervals between dispensing dates
The number of dispensations in the 3, 6, 12 and 13–24 months following the index date were computed. The intervals between dispensations occurring in the first 3 months, between 3 and 6 months, in the first 6 months, between 6 and 12 months, in the first 12 months and in the second year were calculated. Finally, the proportion of patients with at least three dispensations within 3 months of the index date was described, as well as the time period between the last dispensation within those first 3 months and the following one, where applicable.

Treatment switch
The proportion of patients with different IVT anti-VEGF molecules reimbursed during the follow-up and the time between the index date and the first dispensation of a different molecule were evaluated. The number of dispensations before the first switch was calculated.

Treatment monitoring
The number of eye monitoring examinations (i.e. OCT, fluorescein or indocyanine green angiography, dilated fundus and fundus photography) performed during the first and second year following the index date was evaluated overall and by examination type.

Statistical analysis

The analyses were conducted at the patient level, as no distinction between the eyes could be made. The data were analysed descriptively. Qualitative variables were summed up using effectives and percentages in each category and quantitative variables by mean (standard deviation) or median (interquartile range).

For newly treated patients, characteristics related to IVT anti-VEGF use during follow-up were first evaluated in the total sample of initiators. Sensitivity analyses were conducted to assess potential differences according to the molecule initiated and the year of initiation. Additional sensitivity analyses were conducted (i) to exclude patients with only one dispensation during follow-up when describing treatment interruptions and (ii) to assess possible variations in the number of IVT anti-VEGF dispensations and eye monitoring examinations according to the occurrence of a treatment interruption during the first year. Finally, a sub-analysis was conducted among newly treated patients to assess sociodemographic and management characteristics according to likely or possible treatment indications. For patients who had multiple episodes of IVT anti-VEGF initiation during the study period, only the first episode was considered in analyses summarizing the results for the entire study period. Descriptions in the second year of treatment were made among patients with at least two years of follow-up.

The data were computed using SAS guide version 7.15.

Results

A total of 224 775 patients currently treated with ranibizumab or aflibercept in 2018 and 330 969 newly treated patients between 2014 and 2018 were included.

Sociodemographic characteristics and medical history

The sociodemographic characteristics and medical history of patients treated with IVT anti-VEGF are presented in Table 1.

Patients currently treated in 2018
Among current users in 2018 (N = 224 775), the mean age was 78.1 ± 11.3 years, 60% were female, and 12% of those under 65 years of age had complementary universal health insurance. Cardiovascular comorbidities or risk factors were common in this elderly population with retinal diseases (Table 1). Of these patients, 26% had ocular hypertension or glaucoma and 15% had been treated with intravitreal implant, laser

TABLE 1. Characteristics of current users of intravitreal anti-VEGF in 2018 and new users between 2014 and 2018 in France.

Characteristics of patients treated with IVT anti-VEGF	Current users in 2018 N = 224 775	New users 2014–2018 N = 330 969
Sociodemographic characteristics		
Age, years:		
Mean (SD)	78.1 (11.3)	75.9 (12.0)
Median (IQR)	80 (71–86)	78 (69–85)
Age groups, years, *n* (%):		
≤50	4894 (2)	11 348 (3)
51–60	11 736 (5)	24 420 (7)
61–70	34 290 (15)	61 250 (19)
71–80	63 101 (28)	94 650 (29)
81–90	88 085 (39)	116 375 (35)
>90	22 669 (10)	22 926 (7)
Female, *n* (%)	134 475 (60)	193 887 (59)
Complementary universal health insurance[a], *n* (%)	3559 (12)	7136 (12)
Deprivation index (fifths), *n* (%):		
1 (least deprived)	41 215 (18)	57 136 (17)
2	39 132 (17)	56 978 (17)
3	44 987 (20)	65 962 (20)
4	45 368 (20)	67 437 (20)
5 (most deprived)	43 497 (19)	67 062 (20)
Missing	10 576 (5)	16 394 (5)
Non ophthalmological medical history		
Diagnosis, *n* (%)		
Ischaemic heart disease	28 468 (13)	40 400 (12)
Including myocardial infarction	7324 (3)	7319 (2)
Arrhythmia or conduction disorders	26 352 (12)	34 304 (10)
Including non-valvular atrial fibrillation	17 071 (8)	21 793 (7)
Heart failure	13 304 (6)	17 344 (5)
Stroke	8806 (4)	11 516 (4)
Chronic smoking index	28 470 (13)	38 621 (12)
Morbid obesity index	20 864 (9)	32 848 (10)
Chronic alcoholism index	4367 (2)	7177 (2)
Recent diagnosis of cancer	11 303 (5)	15 130 (5)
Treatment, *n* (%)		
Antihypertensive	158 705 (71)	225 890 (68)
Lipid-lowering	93 157 (41)	138 989 (42)
Antiplatelet	78 764 (35)	112 566 (34)
Antidiabetic	58 026 (26)	90 271 (27)
Anticoagulant	31 584 (14)	40 455 (12)
Antiarrhythmic	25 326 (11)	36 323 (11)
Ophthalmologic comorbidities and care		
IVT anti-VEGF indication, *n* (%)		
AMD	170 153 (76)	240 905 (73)
Likely	78 636 (35)	86 422 (26)
Possible	91 517 (41)	154 483 (47)
DME	45 931 (20)	75 839 (23)
Likely	13 803 (6)	23 951 (7)
Possible	32 128 (14)	51 888 (16)
RVO-related macular oedema (likely)	2644 (1)	4261 (1)
Myopic CNV (likely)	1259 (2)	2633 (1)
Mixed indications or not determined	4788 (2)	7331 (2)
Ocular hypertension or glaucoma, *n* (%)	59 192 (26)	61 842 (19)
Treatment sharing IVT anti-VEGF indications		
At least one treatment, *n* (%):	33 226 (15)	48 470 (15)
Intravitreal implant	21 543 (10)	29 461 (9)
Laser photocoagulation	13 559 (6)	21 908 (7)
Photodynamic therapy	1567 (1)	1492 (0)
Eye surgery before IVT anti-VEGF initiation		
≥1 surgery (any location), *n* (%):	–	7042 (2)
Crystalline	–	4951 (1)
Retina	–	147 (0)

photocoagulation or photodynamic therapy before the index date.

Patients newly treated between 2014 and 2018

New users of IVT anti-VEGF between 2014 and 2018 (N = 330 969) were younger (mean age 75.9 ± 12.0 years) and less likely to have ocular hypertension or glaucoma (19%) than current users in 2018. Other characteristics were similar. Two percent of new users underwent eye surgery in the month before the index date. For 96% of new users, eye examinations (OCT, angiography, dilated fundus or fundus photography) were registered between the index date and the previous year (mean number of eye examinations 3.3 ± 3.0), OCT being the most frequently performed.

Characteristics related to current use of IVT anti-VEGF in 2018

Among patients currently treated in 2018 (N = 224 775), the IVT anti-VEGF molecule dispensed at the index date was ranibizumab in 59% of cases and aflibercept in 41%. The main indications for IVT anti-VEGF were AMD (76%, of which 35% were likely and 41% possible indications) and DME (20%, of which 6% were likely and 14% possible indications). Retinal vein occlusion (RVO)-related macular oedema and myopic CNV affected 1% and 2% of patients, respectively. For 2% of patients, the indication for treatment remained undetermined. (Table 1). The prescription came from a private practitioner in 72% of cases (of whom 96% were ophthalmologists) or from a hospital practitioner in 28% of cases. On average, current users who started IVT anti-VEGF before 2018 (N = 148 795, 66%) had a treatment history of 2.9 ± 2.0 years with 13.7 ± 11.8 dispensing dates, and 55% had received the same IVT anti-VEGF molecule. *(Results not shown)*.

Characteristics related to new use of IVT anti-VEGF between 2014 and 2018

Among the 330 969 patients newly treated with IVT anti-VEGF between 2014 and 2018, the maximum follow-up period was 6 years (mean 3.2 ± 1.4 years). Most of them (83%) were followed up until the end of the study period (12-31-2019). Other

TABLE 1 (Continued)

Characteristics of patients treated with IVT anti-VEGF	Current users in 2018 *N* = 224 775	New users 2014–2018 *N* = 330 969
Eye examination before IVT anti-VEGF initiation	–	
≥1 eye examination, *n* (%):	–	318 693 (96)
OCT	–	302 506 (91)
Dilated fundus	–	151 037 (46)
Angiography (fluorescein or indocyanine green)	–	128 184 (39)
Fundus photography	–	56 787 (17)
Total number of eye examinations, mean (SD)	–	3.3 (3.0)

AMD = aged-related macular degeneration, CNV = choroidal neovascularisation, DME = diabetic macular oedema, IQR = interquartile range, IVT = intravitreal, OCT = optical coherence tomography, RVO = retinal vein occlusion, SD = standard deviation.
[a] Calculated among patients aged 65 years or less (*N* = 29 104 current users in 2018 and 59 494 new users between 2014 and 2018).

censoring reasons are presented in Table S2.

Initial dispensing

The number of newly treated patients increased from 60 787 in 2014 to 76 683 in 2018 (+26%) (Fig. 1 and Table S3). The initial prescription was primarily for AMD (73%, of which 26% were likely and 47% possible indications) and DME (23%, of which 7% were likely and 16% possible indications). Retinal vein occlusion (RVO)-related macular oedema and myopic CNV affected 1% of patients as did myopic CNV. For 2% of patients, the indication for treatment remained undetermined. (Table 1). The molecule initiated was ranibizumab in 70% of cases, with a decrease observed over time (76%–69% between 2014 and 2018) in favour of aflibercept. The initial prescription came from a private practitioner in 72% of cases (of whom 96% were ophthalmologists) or from a hospital practitioner in 29% of cases (Table S3).

Duration receiving treatment and treatment interruption

The mean time between IVT anti-VEGF initiation and the last dispensation during the follow-up was 1.6 ± 1.6 years (varying from 2.4 to 0.8 years for new users in 2014 and 2018 respectively). A treatment interruption was recorded for 83% (*N* = 273 699) of newly treated patients and occurred on average of 6.1 ± 8.1 months (median 3, IQR 2-8 months) after treatment initiation (Table 2). Of those who interrupted the treatment, 13% (*N* = 35 264) had only one IVT anti-VEGF dispensation during the follow-up. Sensitivity analysis excluding these patients did not materially change the estimates. (Table S4).

Number of dispensations

The mean number of IVT anti-VEGF dispensations in the 3, 6, and 12 months and the second year following the index date (inclusive) was 2.6 ± 1.0, 3.4 ± 1.6, 4.8 ± 2.8 and 2.2 ± 2.9, respectively (Fig. 2), without differences by year of initiation or molecule initiated. Within the first 3 months, out of a possible maximum of four dispensations per eye treated, 67% of newly treated patients had at least three dispensations of IVT anti-VEGF, with a slightly higher proportion for aflibercept than for ranibizumab initiators (70% versus 65%) *(results not shown)*. In the sensitivity analysis excluding patients with a treatment interruption recorded in the first year (*N* = 233 145, 70%), the mean number of IVT anti-VEGF dispensations was 7.7 ± 2.3 in the first year and 5.2 ± 2.8 in the second year following the index date (Table S5).

Time intervals between dispensing dates

The median (IQR) time intervals between IVT anti-VEGF dispensing dates registered within 3 months, between 3 and

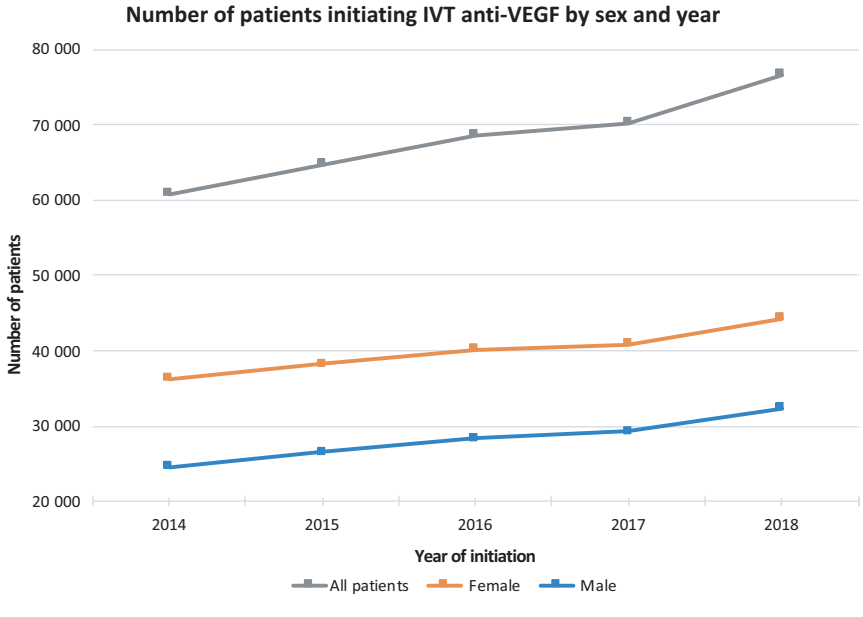

Fig. 1. Number of patients initiating intravitreal anti-VEGF between 2014 and 2018 by sex and year. VEGF = vascular endothelial growth factors.

TABLE 2. Duration receiving intravitreal anti-VEGF treatment and treatment interruption during the follow-up among newly treated patients between 2014 and 2018.

	Newly treated patients by year of initiation					
	2014–2018[a] *N* = 330 969	2014 *N* = 60 787	2015 *N* = 64 674	2016 *N* = 68 592	2017 *N* = 70 241	2018 *N* = 76 683
Follow-up duration						
Mean (SD), year	3.2 (1.4)	4.8 (1.2)	4.1 (0.9)	3.3 (0.6)	2.4 (0.4)	1.5 (0.3)
Median (IQR), year	3.0 (2.0–4.2)	5.2 (4.3–5.6)	4.3 (4.0–4.7)	3.4 (3.1–3.7)	2.5 (2.2–2.7)	1.5 (1.2–1.7)
Time period between initiation of treatment and the last dispensation:						
Mean (SD), year	1.6 (1.6)	2.4 (2.1)	2.0 (1.8)	1.7 (1.4)	1.2 (1.0)	0.8 (0.6)
Median (IQR), year	1.1 (0.2–2.6)	1.8 (0.2–4.8)	1.6 (0.2–3.9)	1.5 (0.2–3.0)	1.2 (0.2–2.1)	0.7 (0.2–1.2)
Time period between initiation and the first interruption[b] of treatment						
Interruption, *n* (%)	273 699 (83)	55 986 (92)	58 062 (90)	59 061 (86)	56 367 (80)	52 237 (68)
Mean (SD), month	6.1 (8.1)	7.5 (10.7)	7.1 (9.4)	6.4 (7.7)	5.3 (5.8)	3.5 (3.4)
Median (IQR), month	3 (2–8)	3 (2–9)	3 (2–9)	3 (2–9)	3 (2–8)	2 (1–5)
Categories, *n* (%[c]), month						
≤3	145 474 (53)	28 668 (51)	29 506 (51)	30 435 (52)	30 140 (54)	31 862 (61)
4–6	41 341 (15)	7700 (14)	8149 (14)	8461 (14)	8572 (15)	9763 (19)
7–12	46 330 (17)	8986 (16)	9553 (17)	10 001 (17)	9892 (18)	9983 (17)
13–18	18 931 (7)	3963 (7)	4288 (7)	4578 (8)	4855 (9)	1629 (3)
19–24	9549 (4)	2211 (4)	2504 (4)	2544 (4)	2363 (4)	0 (0)
>24	12 074 (4)	4458 (8)	4062 (7)	3042 (5)	545 (1)	0 (0)

IVT = intravitreal, IQR = interquartile range, SD = standard deviation, VEGF = vascular endothelial growth factors.
[a] New users of IVT anti-VEGF several times between 2014 and 2018 are counted once and the data relate to the first episode of treatment.
[b] Treatment interruption was defined as a time period of more than 6 months between two IVT anti-VEGF dispensations or between the last IVT anti-VEGF dispensation and the end of follow-up. The interruption date corresponds to the most recent date in these intervals.
[c] Percent of patients with at least one interruption during the follow-up.

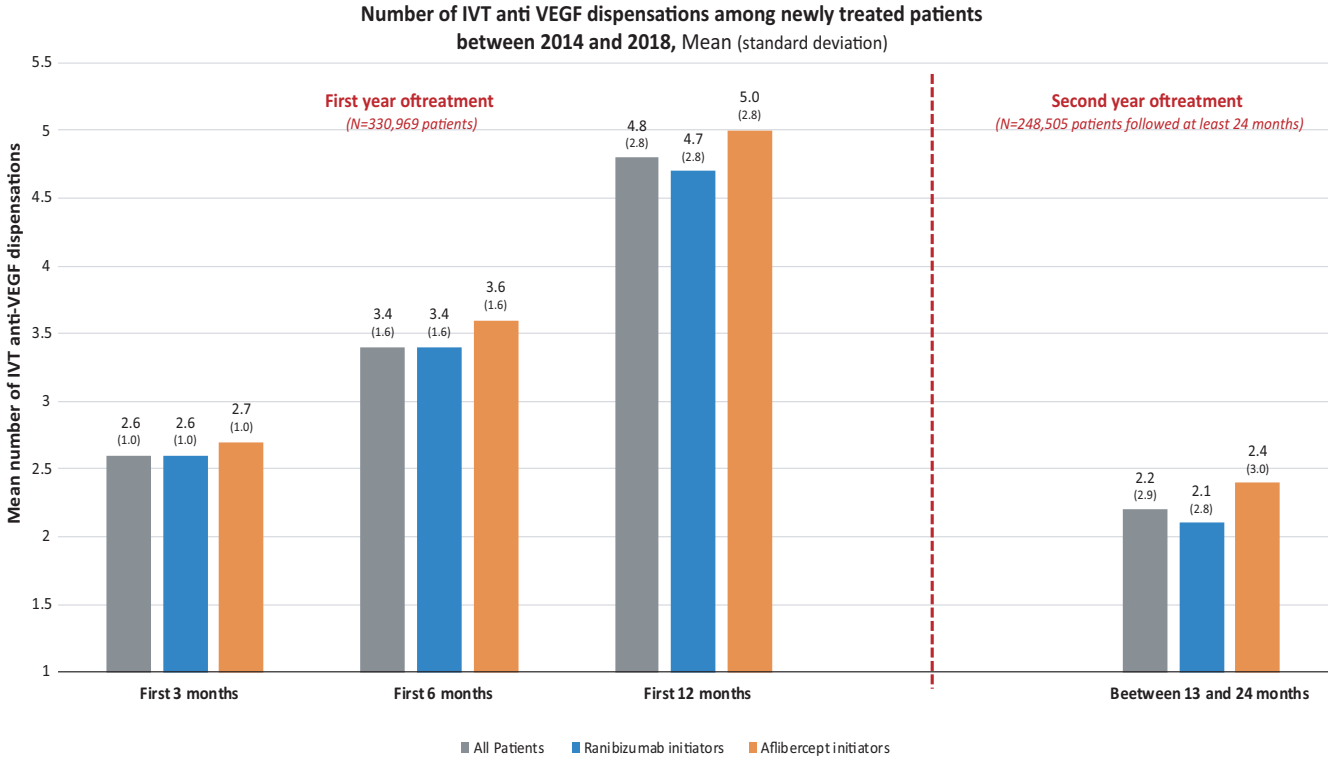

Fig. 2. Mean (SD) number of intravitreal anti-VEGF dispensations in the first and second year of treatment among newly treated patients between 2014 and 2018, by molecule initiated. VEGF = vascular endothelial growth factors.

6 months, between 6 and 12 months and between 13 and 24 months following the index date among newly treated patients with ≥2 IVT anti-VEGF dispensations during the intervals considered, were respectively 31 (28–35), 55 (40–80), 69 (49–106) and 84 (56–143) days. The median (IQR) time between the last dispensation in the first three months

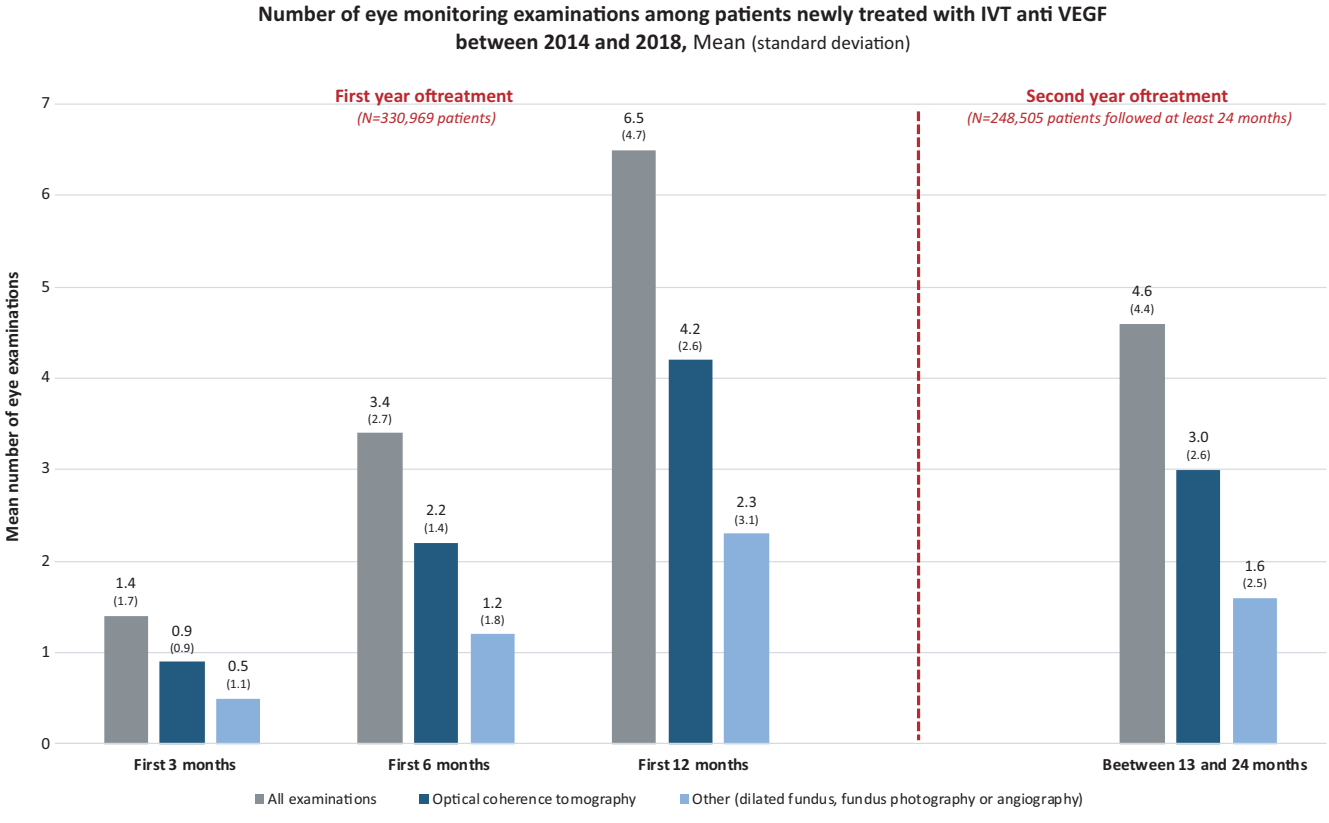

Fig. 3. Mean (SD) number of eye monitoring examinations in the first and second year of treatment among patients newly treated with IVT anti-VEGF between 2014 and 2018, by examination type. IVT = intravitreal; VEGF = vascular endothelial growth factors.

and the following one (where applicable, N = 227 287, 69%) was 2.7 (1.6–5.0) months. No differences were found by year of initiation or molecule initiated. *(Results not shown)*.

Molecule changes

A change of molecule during follow-up was observed in 23.7% (N = 78 317) of newly treated patients. The first change occurred on an average of 13.8 ± 11.0 months after the treatment initiation and on average after 6.2 ± 5.0 dispensations of the initial molecule. Seventy percent of the treatment changes were in favour of aflibercept. *(Results not shown)*.

Treatment monitoring

For 95% (N = 315 941) of patients newly treated with IVT anti-VEGF, an eye monitoring examination had been recorded at least once in the year following the index date (not included). The first eye examination occurred on an average of 69.5 ± 52.4 days after the index date *(Results not shown)*. The mean number of eye monitoring examinations recorded within the 3, 6 and 12 months following the index date were 1.4 ± 1.7, 3.4 ± 2.7 and 6.5 ± 4.7, respectively. Optical coherence tomography (OCT) was the most commonly performed (at least once in the first year for 94% of new users versus 44% for dilated fundus, 19% for angiography and 20% for fundus photography). (Fig. 3).

In the second year of treatment, 83% (N = 205 444/248 505) of patients had at least one eye monitoring examination (mean 4.6 ± 4.4 examinations), with OCT remaining the most commonly performed (Fig. 3). In sensitivity analyses, the mean number of eye monitoring examinations in the second year was 7.4 ± 4.7 in patients without a treatment interruption in the first year (N = 71 123, 29%) and 3.4 ± 3.6 in patients with a treatment interruption in the first year (N = 177 382, 71%) (Table S6).

No differences were found by year of initiation or molecule initiated. *(Results not shown)*.

Sub-analysis by treatment indication

Compared to patients treated for AMD (N = 240 905; 73%), patients treated for DME (N = 75 839; 23%), RVO-related macular oedema (N = 4261; 1%) or myopic CNV (N = 2633; <1%) were younger at treatment initiation (mean age 67.9 ± 13.7 to 71.3 ± 12.8 years versus 77.9 ± 11.4 years), less often female (46%–52% versus 63%) and had more often received an intravitreal implant, laser photocoagulation or photodynamic therapy in the year before IVT anti-VEGF initiation (26%–28% versus 10%). Patients with DME or RVO-related macular oedema were more deprived than other patients. Treatment interruptions were more frequent in patients treated for myopic CNV or DME compared to other patients (92% and 87%, respectively, versus 81%). The time between treatment initiation and its first interruption (if any) was shorter in case of myopic CNV than for other indications (mean 4.2 ± 6.5 months versus 5.6 ± 7.2 to 6.4 ± 8.0 months). Compared to patients treated for other indications, those treated for myopic CNV received fewer IVT anti-VEGF dispensations (mean 3.5 ± 2.6 versus 4.8 ± 2.7 to 3.0 in the first year) and were more likely to receive a single dispensation (25% versus 10–12%) during follow-up. The number

of eye monitoring examinations was almost similar between the indications. Results are presented in Table S7.

Discussion

In this observational study conducted using the French National Health Insurance Databases, a total of 224 775 patients currently treated with IVT anti-VEGF in 2018 and 330 969 patients newly treated between 2014 and 2018 were identified. Ranibizumab was the most frequently prescribed molecule, with a slight decrease observed over time in favour of aflibercept. Cardiovascular diseases or risk factors were frequent among patients treated with IVT anti-VEGF. Main indications for IVT anti-VEGF were AMD (>70%) and DME (>20%). Patients currently treated had a mean number of 13.7 dispensations for a mean duration of 2.9 years. A 26% increase in IVT anti-VEGF initiation was recorded between 2014 and 2018. Among newly treated patients, the mean duration receiving a treatment was 1.6 years. Most of these patients (67%) had at least three dispensations in the first 3 months, suggesting a majority of injection strategies including a loading dose, which is recommended for most treatment indications (European Medicine Agency 2009, 2012). Patients newly treated with IVT anti-VEGF received a higher number of injections and eye monitoring examinations in the first year than in the second year (mean injections 4.8 versus 2.2; mean examinations 6.5 versus 4.6). During the observation period, 83% of newly treated patients had a treatment interruption which occurred on average 6.1 months after initiation. A molecule change occurring within a mean of 13.8 months after the start of treatment and after a mean of 6.2 dispensations was observed for 23.7% of newly treated patients. In 70% of cases the change was observed in favour of aflibercept. Overall, no strong differences in treatment management were observed between patients initiating ranibizumab or aflibercept. Subanalysis by treatment indication showed more treatment interruptions in patients with DME or myopic CNV and fewer injections in patients with myopic CNV compared to other patients.

In our study, patients using IVT anti-VEGF were treated and examined less frequently than (i) in registration randomized clinical trials (RCT) based on monthly injections and surveillance (Brown et al. 2006, Rosenfeld et al. 2006), and (ii) in the PrONTO prospective study based on a reactive approach (i.e. ProReNata-PRN strategy: injection in the presence of disease recurrence depending on visual acuity and results of eye imaging), which has provided similar visual acuity results with fewer injections (i.e. 5.6 IVT injections) than registration RCT, but similar monthly monitoring visits during the first year (Fung et al. 2007). These results, also reported in other real-world studies (Kiss et al. 2020; Mehta et al. 2020) may reflect ophthalmologists' interest in strategies to reduce the clinical burden of IVT anti-VEGF treatment and/or challenge of maintaining regular follow-up in elderly patients (due to difficulties getting to visits, and because healthcare resources are stretched) associated with fewer injections. In our study, the number of IVT anti-VEGF dispensations recorded during the first year in newly treated patients is in line with French studies conducted in nAMD patients: one conducted on 500 eyes recently treated with ranibizumab (Cohen et al. 2013) and another conducted among 586 aflibercept initiators (Weber et al. 2019). Older studies conducted on smaller samples of nAMD patients found a lower number of yearly injections (3.4 and 3.8) (Cohen et al. 2009; Souied et al. 2015). This may reflect a shift towards practices that prefer pro-active strategies (e.g. "treat and extend": intervals between injections increase or decrease, respectively, in the absence or in presence of recurrence) (Spaide 2007; Hufendiek et al. 2018) to reactive strategies (Fung et al. 2007) which require frequent ophthalmological visits and examinations to monitor disease, and are therefore difficult to implement in clinical practice. In fact, pro-active strategies, which generally induce more injections in real-world conditions (Oubraham et al. 2011) than reactive strategies, are most often considered the therapeutic regimen of choice by learned societies (Hufendiek et al. 2018). Several recent observational studies on the use of IVT anti-VEGF for the treatment of nAMD in other countries, based on large databases, have been published. Among 30 106 patients newly treated with IVT anti-VEGF between 2009 and 2016 recorded in the US Retina electronic database, the mean number of injections was 6.0 in the first year and 4.9 in the second year (Kiss et al. 2020). Among 8328 patients registered in the Swedish Macular Registry, newly treated with IVT anti-VEGF between 2012 and 2014, the mean number of injections at 12 months was 6.1 (Westborg et al. 2017). A meta-analysis summarising data of 25 761 eyes newly treated with IVT anti-VEGF between 2010 and 2020 in the UK reported a mean 7.1 of injections in the first year for the most recent publications (Mehta et al. 2020). In these studies, the number of injections in the first years of treatment was higher than in our study. These differences between countries could be explained by variations in the capacity of healthcare systems and/or recommended care practices (e.g. reimbursement and number of injections allowed, eligibility conditions for treatment, time to start treatment etc.).

Overall, no strong differences were observed between patients initiating ranibizumab or aflibercept as reported in other real-world studies (Gillies et al. 2016; Lotery et al. 2017). In fact, there seems to be no rationale in current practice for using one or other of these molecules, as they have similar anti-VEGF properties.

This study, conducted at the scale of the entire French population and benefiting from a long follow-up for new users and extended history for current users of IVT anti-VEGF, provides recent data about the medical history of IVT anti-VEGF users, and patterns of IVT anti-VEGF use in France. Previous studies have most often been conducted on small samples of patients treated with IVT anti-VEGF from specific ophthalmologic practices that may not be fully representative of patient management across the country. The present study also served to evaluate patterns associated with aflibercept use in France; most previous observational studies have been conducted on patients treated with ranibizumab due to its earlier approval. All IVT anti-VEGF dispensations are registered in the SNDS database and the dispensing date is a good approximation of the injection date (the median duration between dispensing and injection dates was 5 days, *results not shown*) because of specific protocols required in France

for the prescription and dispensing of these costly molecules.

This study also has several limitations. First, this study did not aim to describe management characteristics according to IVT anti-VEGF indication, as this information was not directly available in the databases. Although significant efforts were made to estimate the likely or possible indications of IVT anti-VEGF treatments, some misclassification cannot be excluded. Nevertheless, nAMD is the most frequent indication and the overall results largely reflect the management of this disease. Second, these data do not enable to distinguish the IVT anti-VEGF dispensations related to each treated eye, which may have led to an overestimation of the number of injections per treated eye and an underestimation of the intervals between injections per treated eye in the case of bilateral disease with staggered treated eyes. In our study, about 16% of newly treated patients had received more than one unitary box within a timeframe of 3 weeks several times during the first two years *(results not shown)*. This indicator, which could help to estimate the proportion of patients with bilateral disease, suggests that this would only concern a minority of newly treated patients, at least in the first two years of treatment. Third, the SNDS databases are lacking in clinical data to identify potential outcome factors (e.g. disease severity, time since initial diagnosis and management of the disease, treatment efficacy, side effects etc.) that may have influenced ongoing treatment decisions (e.g. reduction, interruption, or discontinuation of the treatment). Finally, these findings may not be representative of the situation in other countries. Indeed, disease management is likely to differ between countries due to varying constraints and incentives associated with the healthcare systems within these countries, including reimbursement, selection of patients for treatment or the number of permitted injections (Holz et al. 2015).

Conclusion

This study, conducted at the scale of the entire French population, reflects the characteristics of patients treated with IVT anti-VEGF and the patterns of use in real-world conditions in France. Initiation of IVT anti-VEGF increased between 2014 and 2018. This study shows frequent treatment interruptions in the first year and a lower number of dispensations and eye monitoring examinations than in pivotal RCT. Other clinical studies using representative samples might be conducted in order to better understand the reasons for frequent treatment interruptions observed in the first year of treatment (e.g. delay in initial management to attain optimal IVT anti-VEGF efficacy, side effects, under-treatment due to clinical burden etc.).

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Marion Bertrand and Sophie Billioti de Gage have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Sophie Billioti de Gage, Mahmoud Zureik. Acquisition, analysis, or interpretation of the data: all the authors. Drafting of the manuscript: Sophie Billioti de Gage. Critical revision of the manuscript for important intellectual content: all the authors. Statistical analysis: Marion Bertrand, Sophie Billioti de Gage. Administrative, technical, or material support: Marion Bertrand. Supervision: Mahmoud Zureik.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Algorithm used to identify comorbid conditions or comedications in the SNDS databases.

Table S2. Duration of follow-up and cause of censoring among patients newly treated with intravitreal anti-VEGF between 2014 and 2018.

Table S3. Patterns of initial dispensing of intravitreal anti-VEGF between 2014 and 2018 in France.

Table S4. Duration receiving intravitreal anti-VEGF treatment and treatment interruption during the follow-up among newly treated patients between 2014 and 2018. Sensitivity analysis excluding those with a single dispensation during the follow-up.

Table S5. Number of intravitreal anti-VEGF dispensations in the first and second year of treatment among newly treated patients between 2014 and 2018. Sensitivity analysis among those without treatment interruption in the first year.

Table S6. Number of eye monitoring examinations in the second year of treatment among patients newly treated with intravitreal anti-VEGF. Sensitivity analysis considering whether or not a treatment interruption occurred during the first year.

Table S7. Sociodemographic, medical and management characteristics of patients newly treated with intravitreal anti-VEGF between 2014 and 2018 in France according to treatment indications.