Pattern of use of intravitreal drugs with antiangiogenic properties for age-related macular degeneration and other vascular retinopathies

Protocol version: 1.2

Title	Pattern of use of intravitreal drugs with antiangiogenic properties for age-related macular degeneration and other vascular retinopathies
Medicinal product(s) / Device(s)	Bevacizumab, Ranibizumab, Pegaptanib, Aflibercept, Dexamethasone
Event(s) of interest	Age-related macular degeneration
Research question and objectives	To describe the pattern of use of intravitreal drugs with antiangiogenic properties for age-related macular degeneration and other vascular retinopathies
Country(ies) of study	Tuscany region, Italy
Protocol author(s)	Giuseppe Roberto (ARS), Francesco Attanasio (UniFi) Gianni Virgili (UniFi), Rosa Gini (ARS), Claudio Marinai (ESTAR)

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LIST OF ABREVIATIONS:

AMD	Age-related Macular Degeneration
Anti-VEGF	Anti-vascular endothelial growth factors
ARS	Agenzia regionale di sanità della Toscana
ESTAR	Ente di supporto tecnico-amministrativo regionale
OCT	Optical coherence tomography
DME	Diabetic Macular Edema
UniFi	University of Florence

RESPONSIBLE PARTIES

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Francesco Attanasio	Careggi Hospital	Pharmacist/ Researcher
Claudio Marinai	ESTAR	Decision maker/Researcher

DOCUMENT HISTORY

Name	Date	Version	Description
Rosa Gini, Gianni Virgili, Giuseppe Roberto, Francesco Attanasio, Claudio Marinai	July 1st, 2016	1.0	First complete version
Claudio Marinai, Gianni Virgili, Andrea Messori, Sabrina Tripoli			Revisions
Rosa Gini	July 5th	1.1	Revised version
Claudio Marinai, Gianni Virgili			Comments and input
Rosa Gini	September 2nd	1.2	Final version

AMENDMENTS AND UPDATES

Version	Description of changes	Study protocol section	Date of effectiveness

ABSTRACT

Background

In the last decade, the development of anti-angiogenic therapy, e.g., intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents, have played an important role in the treatment of neovascular eye diseases, particularly in age-related macular degeneration (AMD), diabetic retinopathy (DR) including diabetic macular edema (DME) as well as proliferative diabetic retinopathy (PDR), and macular edema secondary to retinal vein occlusions (RVO).

Study objective

To describe the pattern of use of anti-VEGF drugs for the treatment of age-related macular degeneration and other vascular retinopathies in clinical practice in Tuscany, Italy.

Study design

This is a descriptive, population-based, pharmacoepidemiological study on the utilization of anti-VEGF drugs for the treatment of age related macular degeneration and other vascular retinopathies in clinical practice.

All subjects registered in the ARS data base between January 1, 2011 and December 31, 2015 and with ≥1 record of intravitreal injection will be recruited. Each record of intravitreal injection will be paired with a drug prescription of Bevacizumab, Ranibizumab, Pegaptanib, Aflibercept, Dexametasone.

We cannot associate to an injection the treated eye.

Main outcomes

We will identify patients with less than 5 injections in the first year: this will be considered an inappropriate utilization for all drugs except Dexamethasone. We will identify patients having a longer interval than 3 months between consecutive contacts with an ophthalmologist: this will be considered inappropriate follow-up. We will identify the true utilization of each drug, in terms of number of injections per year and intra-injections interval. We will perform the same measures in patients with an appropriate follow-up.

BACKGROUND

In the last decade, the development of anti-angiogenic therapy, e.g., intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents, have played an important role in the treatment of neovascular eye diseases, particularly in age-related macular degeneration (AMD), diabetic retinopathy (DR) including diabetic macular edema (DME) as well as proliferative diabetic retinopathy (PDR), and macular edema secondary to retinal vein occlusions (RVO).

Age-related macular degeneration (AMD)

AMD is the leading cause of irreversible blindness in people 50 years of age or older in the developed world (Resnikoff 2004). Although an estimated 80% of patients with AMD have the non-neovascular form (Kahn 1977), the neovascular (wet or exudative) form is responsible for almost 90% of severe visual loss (visual acuity 20/200 or worse) resulting from AMD (Ferris 1984). The hallmark of neovascular AMD is choroidal neovascularization (CNV). CNV is a process which is characterized by the abnormal growth of choroidal blood vessels through Bruch's membrane and into the subretinal space (i.e., under or within the macular, the central portion of the retina responsible for high-resolution vision). These choroidal neovascular vessels leak blood and fluid and forming the characteristic lesion of wet AMD. CNV can be classified by fluorescein angiography into major angiographic patterns termed classic and occult, which may be associated with various degrees of vision loss.

Treatment options for people with neovascular AMD are limited. Although laser photocoagulation and photodynamic therapy (PDT) with verteporfin could be effective in treating lesions for specific subgroups of patients, they do not prevent CNV formation. Anti-angiogenic therapy, e.g., anti-vascular endothelial growth factors (anti-VEGF), which aims to prevent further neovascularization rather than only destroy it, is the latest approach to the treatment of neovascular AMD. Four intravitreal anti-VEGF therapies are available for the treatment of neovascular AMD. The first anti-VEGF approved in 2004 by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for neovascular AMD was intravitreal Pegaptanib sodium (Macugen; PharmaSwiss Ceská republika s.r.o. Jankovcova 1569/2c 170 00 Praha 7 Repubblica Ceca). Pegaptanib is an aptamer and selectively binds to VEGF165. A reduced risk of visual acuity loss was observed after IVP injections and improvement of VA occurred only in a small number of eyes. Currently, the most commonly used VEGF antagonists are Ranibizumab (Lucentis; Novartis Europharm Limited Wimblehurst Road Horsham West Sussex, RH12 5AB Regno Unito) and Bevacizumab (Avastin; Roche Registration Limited 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW Regno Unito). Ranibizumab, which is an antibody fragment from the bevacizumab molecule with an increased binding affinity for all forms of VEGF, has been approved for the treatment of all angiographic subtypes of subfoveal neovascular AMD by the FDA and by the EMA since 2006 and 2007, respectively. The approval was based on two randomised controlled trials (RCTs) which showed that approximately 95% of the patients treated with monthly ranibizumab injections lost fewer than 15 letters in 12 months, compared to 64% of patients receiving PDT and

62% receiving sham treatment (Rosenfeld 2006; Brown 2006). In contrast to Ranibizumab, Bevacizumab was not developed for the treatment of AMD and consequently has no approval for this use. Bevacizumab is approved for the treatment of specific cancers, e.g., metastatic colon and rectum cancer. Even before Ranibizumab was licensed, Bevacizumab had been used as an off-label treatment for AMD. The first report of intravitreal Bevacizumab administration for neovascular AMD was published in 2005 (Rosenfeld 2005). After this initial report, numerous case series which (apparently) support the efficacy and safety of bevacizumab were published. Aflibercept (Eylea, Regeneron-Bayer HealthCare) is a new, fully human, recombinant fusion protein designed to bind all isoforms of VEGF-A, as well as placental growth factor, which has been evaluated in phase III trials on patients with neovascular AMD (Heier 2012). Aflibercept has been approved by the FDA as well as by EMA for use in AMD in 2012. The relative effectiveness of aflibercept vs ranibizumab in age-related macular degeneration and, more recently, in diabetic macular edema has been a matter of controversy. The VIEW-1 and VIEW-2 studies showed the non-inferiority of aflibercept in age-related macular degeneration (Heier 2012). Based on the above mentioned evidence, and upon request, AIFA has provided Tuscany with a formal assessment that Ranibizumab and Aflibercept are equivalent in terms of efficacy and safety, for the registered indications. In diabetic macular edema, a randomized trial (Diabetic Retinopathy Clinical Research Network, 2015) has found the superiority of aflibercept in a clinically relevant patient subgroup (patients with initial visual-acuity letter score of 20/50 or worse).

Diabetic retinopathy (DR)

Diabetic retinopathy (DR) is the most prevalent retinal vascular disease and a severe ocular complication of diabetes mellitus. It is the leading cause of blindness in the working age population in developed countries (Frank 2004). The prevalence of DR increases with duration of diabetes,(Yau 2012) and nearly all persons with type 1 diabetes and more than 60% of those with type 2 have some retinopathy after 20 years.

Diabetic retinopathy can be classified into 2 stages: nonproliferative and proliferative. The earliest visible signs in nonproliferative DR are microaneurysms and retinal hemorrhages. Proliferative DR occurs with further retinal ischemia and is characterized by the growth of new blood vessels on the surface of the retina or the optic disc. These abnormal vessels may bleed, resulting in vitreous hemorrhage, subsequent fibrosis, and tractional retinal detachment.

Diabetic macular edema (DME), which can occur at any stage of DR, is a frequent manifestation of DR and an important cause of impaired vision in individuals with diabetes (Yau 2012, Frank 2004). DME is the swelling of the retina resulting from the exudation and accumulation of extracellular fluid and proteins in the macula (Ciulla 2003) due to the breakdown of the blood-retina barrier and an increase in vascular permeability (Antcliff 1999). The prevalence of DME is 3% in mild non-proliferative retinopathy, and rises to 38% in eyes with moderate to severe non-proliferative retinopathy, eventually reaching 71% in eyes with proliferative retinopathy. Factors such as the duration of diabetes, hypertension, insulin dependence, glycosylated haemoglobin levels and the

presence of proteinuria (abnormal presence of proteins in urine) have all been implicated in the development of DME (Klein 1984).

Various therapeutic approaches, including laser photocoagulation (which has been the standard of care for DME before Ranibizumab was licensed), pars plana vitrectomy, and intravitreal steroid injections aim to prevent or delay vision loss (EDTRS 1985, Nasrallah 1988, Jonas 2003, Loewenstain 2006). However, unsatisfactory outcomes are frequent, and have often prompted interest in other treatments options for DR. VEGF has been identified as one of the growth factors causing breakdown of the blood–retinal barrier with increased retinal permeability by affecting the endothelial tight junctions (Grant 2004). While the normal human retina contains VEGF, the levels are significantly elevated in eyes with DME (Aiello 1994, Funastu 2002). As a result, pharmacologic attenuation of the effects of VEGF using the VEGF inhibitors Pegaptanib, Ranibizumab and Bevacizumab have been investigated in DR. Pegaptanib was the first anti-VEGF drug reported to have a favorable effect on DME (Sultan 2011). However, the first VEGF inhibitors that was licensed for the treatment of DME is Ranibizumab. Approval for Ranibizumab for the treatment of DR was based on data from two randomised Phase III trials, which demonstrated that Ranibizumab provides superior vision gains compared to laser photocoagulation and sham.(Massin 2010. Mitchell 2011) At one year, the RESTORE results show that on average 37% of people treated with Ranibizumab 0.5 mg alone, and 43% of those treated with Ranibizumab plus laser therapy, gained a substantial vision improvement of 10 letters or more versus 16% of people treated with laser alone. These data also support the earlier results of the RESOLVE study comparing Ranibizumab to sham treatment.

Retinal vein occlusion (RVO)

Retinal-vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy (Campochiaro 2010) and a common cause of vision loss in older persons. There are two distinct types of RVO, classified according to the site of occlusion: (1) In branch retinal vein occlusion (BRVO), the occlusion is typically at an arteriovenous intersection; (2) in central retinal-vein occlusion (CRVO), the occlusion is at or proximal to the lamina cribrosa of the optic nerve, where the central retinal vein exits the eye. CRVO may be ischaemic or non-ischaemic.

RVO has a prevalence of 1 to 2% in persons older than 40 years of age and affects 16 million persons worldwide (Rogers 2010). Bilateral RVO is uncommon (occurring in about 5% of cases), although in 10% of patients with RVO in one eye, occlusion develops in the other eye over time (CVOS Group 1997). BRVO is four times as common as CRVO. In a population-based cohort study, the 15 year incidence rate is estimated to be 1.8% for BRVO and 0.5% for CRVO (Kiire 2012). The ischemic subtype of CRVO accounts for approximately 20% of acute presentations and is associated with a poor visual prognosis (CVOS Group 1997). The non-ischemic type has a better visual prognosis, but may convert to the ischemic type in an estimated one-third of cases within three years, and conversion is most frequent in the initial four months (CVOS Group 1997).

The strongest risk factor for RVO are hypertension and age over 50, but associations have been reported for diabetes mellitus, dyslipidemia,15 cigarette smoking,2 and renal disease. For CRVO, an additional ocular risk factor is glaucoma or elevated intraocular pressure, which may compromise retinal venous outflow (MacDonald 2014).

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Management of macular oedema secondary to RVO: Macular oedema, thought to be caused by leakage of fluid from capillaries in the central macular area, is the most common cause of visual loss in patients with RVO, and a wide range of treatments e.g., laser photocoagulation, steroids as well as intravitreal infection of anti-VEGF have been adopted.

Description of the intervention

Monoclonal antibodies against VEGF were first developed as an intravenous treatment for metastatic colorectal cancer (Homsi 2007).The first drug licensed for this purpose was bevacizumab (Avastin®), which received Food and Drug Administration (FDA) approval in February 2004. Bevacizumab is a 149kDa recombinant humanized monoclonal whole immunoglobulin G1 antibody that binds to VEGF and blocks the binding of VEGF to receptors (Flt-1 and KDR) on endothelial cells. Pegaptanib sodium (Macugen ®) is a 50kDa aptamer; a pegylated modified oligonucleotide, which adopts a three-dimensional configuration in vivo which allows it to bind to extracellular VEGF-165 and antagonize its biological effects (Eyetech 2008; Gragoudas 2004). It was approved by the FDA in 2004 for use in neovascular age-related macular degeneration (Eyetech 2008). Ranibizumab (Lucentis®) was subsequently approved by the FDA for the treatment of neovascular age-related macular degeneration in June 2006. Ranibizumab is a 48kDa recombinant humanized monoclonal immunoglobulin G1 antibody fragment (kappa isotype) that binds to the receptors of biologically active VEGF-A, including VEGF-110. This blocks the binding of VEGF-A to VEGFR1 and VEGFR2 receptors on endothelial cells (Genentech 2008). The pharmacokinetics of 1.25 mg bevacizumab and 0.5 mg ranibizumab intravitreal injections have been investigated in an experimental rabbit model (Bakri 2007). The vitreous concentration of both drugs declined in a monoexponential function, with a half-life of 4.32 days for bevacizumab, and 2.88 days for ranibizumab. Another study found half-life was similar for aflibercept and ranibizumab and respectively 2.3 and 2.2 days (Niwa 2015). Animal models showed that the vitreous concentration of dexamethasone follows two distinct phases after Ozurdex implant: a high concentration phase from 7 to 60 days (peak 213 ± 49 ng/mL measured at day 60) followed by a low concentration phase with detectable levels until day 180 (0.00131 ± 0.00194 ng/mL).

Vascular endothelial growth factor is a cytokine that promotes vascular leakage and growth. Therefore, VEGF inhibiting drugs can be used to treat choroidal neovascularization in AMD and other diseases, as well as macular edema due to diabetic retinopathy and RVO.

However, the growth of blood vessels is part of the normal healing and maintenance of our body. The body, in fact, grows new blood vessels in wound healing and as collateral circulation around

blocked blood vessels. The concern is that these agents will potentially interfere with these normal processes and worsen conditions like coronary or peripheral artery diseases.

STUDY OBJECTIVE

To describe the pattern of use of anti-VEGF drugs for the treatment of age-related macular degeneration and other vascular retinopathies in clinical practice in Tuscany, Italy.

MATERIALS AND METHODS

Study design

This is a descriptive, population-based, pharmacoepidemiological study on the utilization of anti-VEGF drugs for the treatment of age related macular degeneration and other vascular retinopathies in clinical practice.

We will identify inappropriate utilization: excluding Dexamethasone, less than 5 injections in the first year, inappropriate follow-up.

We will describe the true utilization of each drug, in terms of number of injections per year and intra-injections interval. We will perform the same measures in patients with an appropriate follow-up. The rationale for this is that in patients with an appropriate follow-up the choice of delaying an injection is expected to be associated with a better outcome of the treatment.

Setting

Italy has a tax-based, universal coverage National Health System organised in three levels: national; regional (21 regions); and local (on average 10 Local Health Units, LHUs). Healthcare is managed for every inhabitant by the LHU where he/she has her regular address. In the Tuscany region up to 2015 there were 12 LHUs.

Care is provided both by facilities belonging to the LHUs (LHU hospitals) and by other facilities. Among them, Tuscany has 3 University Hospitals (UHs): Careggi from Florence, Scotte from Siena and Cisanello from Pisa.

Data sources

This study will be based on the analysis of the ARS databases which collects pseudonymized patient-level information on the utilization of healthcare services dispensed to all subjects who are residents and registered with a general practitioner in Tuscany, corresponding to a population of around 3.5 million people. For each subject in the data base, demographic information, such as age, sex and pertinent Local Health Authority, can be linked to different registries in which different types of healthcare services reimbursed by the National Healthcare Service are recorded. These include

- Inhabitant Registry (IR) with demographic information (birthyear, gender, citizenship) and start and end dates of presence in the Tuscany region
- hospital discharge records (HOSP): each hospital admission is described with dates of admission and discharge, and one main and five secondary diagnoses and 6 procedures coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9CM);
- outpatient care records (OUTPAT): it is a list of outpatient activities dispensed by the healthcare system free of charge or upon co-payment, among which specialist encounters (with no diagnostic code), laboratory or instrumental or bio-imaging diagnostic tests (without results) and procedures in outpatient setting, recorded with a specific Italian coding system; the facility where the activity takes place is recorded as well
- prescribed drugs intended for outpatient use. Prescription records include information on the dispensed drugs (e.g. active principle, ATC code) as well as the date of dispensation. Drugs are registered in two databases: one collects dispensings from hospital pharmacies (DDRUG), the other dispensings from community pharmacies (DRUGS)
- Disease-specific exemptions from copayment to health care coded using ICD9CM (EXE);

Moreover, ARS collects aggregated data on drugs dispensed during inpatient care (DRUGINP). A record of this table refers to a specific amount of a specific drug that was provided to a specific hospital ward on a specific day.

Study population

All subjects registered in IR between January 1, 2011 and December 31, 2015 will be considered.

The study population will correspond to all subjects active into the data base and with at least 365 days of look-back period or enrolled at birth.

Within such population, all subjects with ≥1 record in OUTPAT of intravitreal injection received in one of the three UHs or in one of the LHU hospitals will be identified.

Each record of intravitreal injection will be paired with a drug prescription of Bevacizumab, Ranibizumab, Pegaptanib, Aflibercept, Dexamethasone from DDRUG.

In case the record linkage between OUTPAT and DDRUG fail in a significant share of the study population, an ancillary descriptive analysis of the overall dispensings of the different drugs will be performed using DRUGINP.

Study variables

Each incident patient will be characterized with drug of first injection, age, gender, citizenship, education level, economic status, comorbidities, proxies for diabetes, glaucoma, recent use of ophthalmologic services, number of years available of followup. To classify indication for use we will identify subjects who at the first cycle are younger than 55 or have a record referred to diabetes (T1 or T2) in exemption registry or hospital discharge record or are in treatment with antidiabetic drugs or a history of use of specific tests for diabetic retinopathy (argon laser test).

As a proxy of appropriate monitoring in the first year we will associate to each patient the following events from OUTPAT (see in the Addendum 1 the specific codes)

- oculistic encounters
- optical coherence tomography
- fluorescence imaging
- imaging of fundus oculis

Patients with no more than 3 months between one event and the following will be considered to be with an appropriate follow-up.

We will identify the load cycle as a sequence of 3 injections with less than 45 days of interval. We will identify patients with a second load cycle and with too short intervals (less than 25 days) as candidate binocular patients.

Main outcomes

To each incident patient we will associate the number of injections per year in the 1st, 2nd, 3rd year (where data available) per starting drug, as well as switching (both within the load cycle of 3 injections and after that). In patients with more than one injection we will calculate the number of days between consecutive injections.

Statistical analysis

We will associate to each starting drug the number of patients, and the percentage of females, of each age band, of year of start and of all the covariates.

For each starting drug we will describe the follow up: distribution of the number of injections and of number of diagnostic contacts in the first year, the percentage of patients with appropriate follow-up in the first year, with at least 2, 3 and 5 injections if the first year, with a proper loading dose (<=45 days between one dose and the other, only patients with >=3 injections), with a switching during loading dose (among patients with >=3 injections), with switching after the loading dose (among patients with >=4 injections), with a second loading dose, with a too short interval between two doses

For each starting drug we will describe the number of injections per year (median, IQ) and the mean interval between injections among patients with at least 3 injections, no switching and no change of hospital. We will then restrict to patients with no suspect binocularity. Finally we will restrict to patients with appropriate follow-up.

The last analysis will be repeated per start year of the therapy. If needed, statistical adjustment will be performed.

See mock tables in Addendum 2.

Data management and processing

Data will be analyzed using the software and statistical software STATA version 12.1.

Limitations of study methods

Specialist encounters and diagnostic exams may have been performed outside of the reimbursement schemas of the National Healthcare Service. This is more likely to have happened in the strata of the population with a higher socio-economic status.

We were not able to associate to a injection the treated eye.

Ethical considerations

The study was approved by the governance board of ARS.

Disseminations and communication strategy

The findings from this study will be submitted to a peer-review international journal before December 2016.

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Addendum 1. Relevant codes

From DDRUG[1]

aflibercept S01LA05 L01XX44
bevacizumab L01XC07 (records coded as '0G00126001', that is ‘galenic preparation’)
ranibizumab S01LA04
dexamethasone A01AC02 C05AA09 D07AB19 D07XB05 D10AA03 H02AB02 H02AB02 R01AD03 S01BA01 S01CB01 S02BA06 S03BA01
pegaptanib S01LA03

from OUTPAT

Intravitreal injection

PP1035 CV INIEZIONE INTRAVITREALE di sostanze terapeutiche (escluso farmaco) 14.79.1

Optical coherence tomography

PP1030 CV OPTICAL COHERENCE TOMOGRAPHY (OCT): Tomografia a coerenza ottica, analizzatore retinico 95.17

Specialist encounter

143500 CO VISITA SPECIALISTICA OCULISTICA 95.02

14350C CO VISITA DI CONTROLLO OCULISTICA 89.01

143400 CO ESAME PARZIALE DELL'OCCHIO Esame dell'occhio con prescrizione di occhiali 95.01

800450 CV FLUOROANGIOGRAFIA O FLUOROANGIO-SCOPIA CON INDOCIANINA 95.12.1

137600 DV FLUOROANGIOGRAFIA O FLUOROANGIO-SCOPIA DELLA CORIORETINA 95.12

137700 CV FOTOCOAGULAZIONE ARGON (LASER) PER PATOLOGIA RETINICA (PER SEDUTA) 14.34

[1] In our query we used both ATC for ophthalmic indications and for other indications, in order to obtain a more sensitive search strategy. The indication is always ophthalmic because we associcated the dispensing with a specific intravitreal injection.

138200 CV FOTOGRAFIA DEL FONDO O SEGMENTO ANTERIORE 95.11.1

Addendum 2. Mock tables

Box 1. Flow chart

Injections
N of injections 2011-2015 N (%) linked to drug N (%) linked to person in Inhabitant Registry
Persons
N of persons with at least one prescription 2011-2015 N (%) in Inhabitant Registry, resident in Tuscany

Table 1. Description of the cohort, per drug utilized during the first injection

		aflibercept	ranibizumab	bevacizumab	dexamethasone	pegaptanib	Missing	Total
N								
F								
Age (mean, sd)								
Ageband	0-44							
	45-54							
	55-64							
	65-74							
	75-84							
	85+							
Citizenship	Italian							
	From countries with high migration pressure							
	From countries with low migration pressure							
	Missing							
Proxies for indication	Use of antidiabetic drugs OR exemption OR discharge diagnosis							
	Glaucoma exemption							
	55 or younger at first injection							
	Argon laser test							
	At lest one of the previous							
Comorbidities	Use of statins							
	Use of antihypertensives							
	Use of antithrombotics							
Use of ophtalmic services in 365 days before	optical coherence tomography (OCT)							
	Specialist encounter							
	Fluorescence imaging with indocyanine							
	Chorioretina							
Year start	2011							
	2012							
	2013							
	2014							
	2015							
Years of follow-up since first injection	1							
	2							
	3							

Hospital of first injection (in parenthesis: % of patients who change hospital during follow-up)	UH Florence							
	UH Siena							
	UH Pisa							
	LHU1							
	…							
	LHU12							

Table 2. Description of the follow-up (only in the population with same hospital and non missing first drug)

		aflibercept	ranibizumab	bevacizumab	dexamethasone	pegaptanib	Total
N							
Number of injections during the first year	1						
	2						
	3						
	4						
	5						
	6						
	7						
	8						
	9						
	10						
	11						
	12						
	>12						
Distribution of diagnostic contacts during the first year	1						
	2						
	3						
	4						
	5						
	6						
	7						
	8						
	9						
	10						
	11						
	12						
	>12						
Patients with appropriate follow-up in the first year	In year 1						
	In year 2						
	In year 3						
Patients with at least x injections during the first year	>=2						
	>=3						
	>=5						
First 3 doses are a loading dose (<=45 days between one dose and the other, only patients with >=3 injections)							
Switchers during loading dose (among patients with >=3 injections)							
Switchers (among patients with >=4 injections)							
% of patients with a new loading dose (among patients with >=3 injections, same hospital)	In year 1						
	In year 2						
	In year 3						
% of patients with a too short interval (<=25 days)	In year 1						
	In year 2						
	In year 3						
Distribution of diagnostic contacts during the first year	1						
	2						
	3						
	4						
	5						
	6						
	7						
	8						

Table 3. Number of injections, intra injection interval, in patients with >=3 injections, without switching

		aflibercept	ranibizumab	Bevacizumab	dexamethasone	pegaptanib	Total
N							
number of injections per year (median, IQ range)	In year 1						
	In year 2						
	In year 3						
Intra injection interval (mean)	In year 1						
	In year 2						
	In year 3						
Number of injections per year (median, IQ range) before new loading dose or short interval	In year 1						
	In year 2						
	In year 3						
Intra injection interval (mean) before new loading dose or short interval	In year 1						
	In year 2						
	In year 3						
Number of injections in patients with >=5 contacts during the first year	In year 1						
	In year 2						
	In year 3						
Intra injection interval (mean) in patients with >=5 contacts during the first year	In year 1						
	In year 2						
	In year 3						