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

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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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DOCUMENT HISTORY

Name	Date	Version	Description
Rosa Gini	October 2nd, 2016	1.0	First version
Andrea Messori, Gianni Virgili			Observations
Rosa Gini	October 27th, 2016	1.1	New version
Andrea Messori, Gianni Virgili			Observations
Rosa Gini	November 17th, 2016	1.2	New version

AMENDMENTS TO THE STUDY PROTOCOL

Version	Description of changes	Comments
1.2	Analysis during the second and third year of follow-up could not be performed due to the low number of patients in aflibercept having more than one year of follow-up	
1.2	The proxy of binocularity was revised due to a mistake in the protocol and is now ‘3 injections in less than 55 days or 2 injections in less than 25 days’	
1.2	The subgroup of users with appropriate follow up was extended to users with at least 5 contacts, in order to allow exploration of time trends	

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, has 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.

Methods

This was 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 were recruited. Each record of intravitreal injection was paired with a drug prescription of bevacizumab, ranibizumab, pegaptanib, aflibercept, or dexamethasone, whenever the linkage was possible. We identified the true utilization of each drug, in terms of number of injections per year and between-injections interval. We performed the same analysis in several subgroups: those who at baseline where not associated with diabetes, and those who had at least 3 injections and a sufficiently intense follow-up in terms of contacts with ophthalmic services.

Results

We identified 13,267 incident users of intravitreal injections in 2011-2015, and we could link to the inhabitant registry of residents 11,377 (85.6%) of them. While 42.7% could not be linked to a drug, of the remaining 6,510 incident users 53.6% were linked to ranibizumab, 28.9% to bevacizumab, 9.0% (from 2013 only) to aflibercept, 7.6% (from 2012 only) to dexamethasone, 0,8% to pegatnanib. The share of users with a proxy of diabetes-related eye disease was smaller among aflibercept users (20.3%), and was 36.9, 39.6 and 45.6 in users of ranibizumab, dexamethasone and bevacizumab, respectively.

We identified a subpopulation of 4,074 incident users from 2011 to 2014 that could be linked to a drug and had one year of follow-up, mostly assisted by University Hospitals and LHU 11. Among them, 57.6% of users of dexamethasone and 40.1% of bevacizumab users had just one application. At least 3 injections were given to 87.2% of aflibercept, 72.1% of ranibizumab and 40.4% of bevacizumab users. A large majority of users had more than 5 contacts in the first year of follow-

up. In this cohort, among those with at least 3 injections, the mean number of injections was 4.1 for aflibercept, 4.0 for ranibizumab and 3.7 for bevacizumab. Mean interval between injections was 52.9 days for ranibizumab, 56.9 days for aflibercept and 61.7 days for bevacizumab users.

Conclusion

Pattern of use of aflibercept and ranibizumab during the first year of utilization were similar in the Tuscan population during the study period. Bevacizumab was often used for one or two injections only. Longer follow-up will allow to compare the drugs in the second and third follow-up year. Access to medical records may allow to investigate comparative efficacy.

BACKGROUND

In the last decade, the development of anti-angiogenic therapy, e.g. intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents, has 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 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 form 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 Czech Republic). 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 has 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 factors for RVO are hypertension and age over 50, but associations have been reported for diabetes mellitus, dyslipidemia, cigarette smoking, and renal disease. For CRVO, an additional ocular risk factor is glaucoma or elevated intraocular pressure, which may compromise retinal venous outflow (MacDonald 2014).

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 and 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 was 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 described the true utilization of each drug in the first year, in terms of number of injections during the year and mean interval between consecutive injections, in a population of patients who are regularly seen by an ophtalmologist (at least 5 contacts with the ophthalmologist service). We performed the same analysis in several subpopulations. The rationale for this is that the choice of delaying an injection is expected to be associated with a better outcome of the treatment, as recommended in the summary of the product characteristics of both Lucentis and Eylea, provided the patient is regularly seen by an ophthalmoligist. (EMA-Lucentis), (EMA-Eylea).

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 they have their 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 was based on the analysis of the ARS databases, which collect 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, Nineth 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 were considered. The study population corresponded 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 were identified.

Each record of intravitreal injection was associated with a drug prescription of bevacizumab, ranibizumab, pegaptanib, aflibercept, dexamethasone from DDRUG.

Study variables at baseline

Each incident patient was 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. As a proxy of indication for use, we identified 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 on treatment with antidiabetic drugs or a history of use of specific procedures for diabetic retinopathy (argon laser). We classified the patients lacking those proxies as "patients with no evidence of diabetes-related neovascular eye disease".

Study variables during follow-up

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

- ophthalmologic examinations

- optical coherence tomography

- fluorescence imaging
- imaging of fundus oculis

Patients with no more than 3 months between one event and the following were considered to be with an appropriate follow-up. We considered a second, wider cohort of patients with 5 or more contacts during the year of follow-up.

We identified patients with a sequence of 3 injections over an interval of less than 55 days and with too short intervals (less than 25 days) as candidate binocular patients.

Main outcomes

To each incident patient with at least 1 year of follow-up we associated the number of injections, as well as switching (both within the loading dose of 3 injections and after that). In patients with at least three injections, we calculated the mean between-injections interval, that is, the mean number of days between consecutive injections.[1]

Statistical analysis

We associated to each starting drug the number of incident patients in 2011-2015, and the percentage of females, of each age band, of year of start and of all the covariates. The same analysis was performed for patients whose injections could not be linked to a drug.

For each starting drug we described the incident patients in 2011-2014, with their covariates, and their follow up in the first year: distribution of the number of injections and of number of diagnostic contacts, percentage of patients with appropriate follow-up, with a loading dose within 90 days, with a switching during loading dose, with switching after the loading dose, with a proxy of binocularity (second loading dose or with a too short interval between two doses)

For each starting drug we described the number of injections in the first year (mean, IQ) and the mean between-injections interval among patients with at least 3 injections, no switching and no suspect binocularity. We repeated the analysis on several subgroups:

- patients with appropriate follow-up (persistent contacts)
- patients with appropriate follow-up (at least 5 contacts, both pooled years and per year)
- patients with no evidence of diabetic-related eye disease (both pooled years and per year)
- patients with more than 3 injections (in this subgroup the interval was computed after the 3rd injection, both pooled years and per year)

Data management and processing

Data were analyzed using the software and statistical software STATA version 12.1.

[1] For instance in the case of a patient with 3 injections in dates D1, D2 and D3, the intervals are D2-D1 and D3-D2. The mean between-injections interval is ((D2-D1)+ (D3-D1))/2=(D3-D1)/2

Ethical considerations

The study was approved by the governance board of ARS.

RESULTS

Study population (Box 1)

In the period 2011-2015, 58,198 injections were recorded in OUTPAT, 50,564 (86.9%) could be linked to IR and 36,399 (62.5%) could be linked to both IR and a drug. In the same period the prevalent users were 16,617, and the incident users were 13,267. Among those, 11,377 (85.6%) could be linked to IR and had at least 365 days of look-back and entered the first analysis.

Incident users in 2011-2014 were 10,041, and 4,074 (40.6%) could be linked to IR, had at least 365 days of look back and at least 365 days of follow-up, and had all their injections linked to a drug dispensing and entered the second analysis.

Description of incident users 2011-2015 (Table 1)

Of the 11,377 incident users that could be linked to IR, 4,867 (42.7%) did not have their first prescription linked to a drug. Of the remaining 6,510 incident users, 3,490 (53.6%) were linked to ranibizumab, 1,885 (28.9%) to bevacizumab, 587 (9.0%, from 2013 only) to aflibercept, 497 (7.6%, from 2012 only) to dexamethasone and 51 (0,8%) to pegaptanib. Due to small numbers, we did not describe the pegaptanib cohort (see Table 1).

Female users were the majority in all exposure strata, except dexamethasone. Aflibercept users were older (respectively 78.7 and 76.9 mean age, compared with 73.3 in ranibizumab, 70.1 in bevacizumab and 69.9 in dexamethasone users)

Citizenship was missing in the large majority of the cohort, independently on the exposure drug or missing, and education was missing in a large share. There was no clear difference among exposure strata as far as non missing data is concerned.

The share of users with a proxy of diabetes-related eye disease was smaller among aflibercept users (20.3%), and was 37.2, 40.2 and 45.7 in users of ranibizumab, dexamethasone and bevacizumab, respectively. The percentage of users with glaucoma ranged from 3.8 in dexamethasone to 6.0 in aflibercept.

There were no major differences in the distribution of use of antihypertensives (from 57.3 to 65.2%), statins (from 63.8 to 70.9%) and antithrombotics (from 9.5 to 74.7%).

The large majority of users had a record of an encounter with an ophthalmologist in the 365 days before the first injection (from 81.1% in ranibizumab to 85.5% in aflibercept). Users of bevacizumab more often started their treatment in 2011 (32.0%), while users of ranibizumab were more equally distributed across the 5 years. Users of dexamethasone were mostly concentrated in

2013, 2014 and 2015, while aflibercept users were mostly concentrated in 2015 (60.0%) and 2014 (35.4%). Loss to follow-up was negligible: number of years of follow-up was only determined by availability of data (available until the end of 2015).

Users with missing first drug had characteristics similar to bevacizumab and ranibizumab users.

The only exception was hospital of first injection: aflibercept users were mostly concentrated in the Florence UH (77.7%), while for the other drugs users were uniformly distributed across the 3 UHs and in the LHU11 hospital. The users with missing drug were mostly concentrated in UH Firenze (16.4%), LHU 8 Arezzo (16,2%), LHU3 Pistoia (15.7%), LHU 6 Livorno (11.9%) and LHU 12 Viareggio (10.4%).

Description of incident users 2011-2014 and of their first year of follow-up (Table 2)

Of the 4,074 users in this subpopulation, 2,160 (53.0%) had a first prescription of ranibizumab, 1,404 (34.4%) of bevacizumab, 255 (6.2%) of dexamethasone, 226 (5.5%) of aflibercept and 29 (0.7%) of pegaptanib. Due to small numbers, we did not describe the pegaptanib cohort (see Table 2).

The baseline characteristics of this subpopulation were similar to the characteristics of the general study population, with few exceptions: aflibercept users were mostly concentrated in year 2014 (88.9%) and in UH Firenze (95.6%).

During follow-up a possible change of eye was detected for 5.6% and 5.8% of users of, respectively, ranibizumab and aflibercept, and for 7,3% of users of bevacizumab. The majority of users of dexamethasone (57.6%) had one intervention only, while users of bevacizumab with a single injection were 40.7%, much more than ranibizumab and aflibercept single-injection users (17.7% and 9.7% respectively). Users with at least 3 injections were 87.2% for aflibercept, 72.1% for ranibizumab, 40.4% for bevacizumab, 16.7% for dexamethasone, and users whose first 3 injections took place within 90 days were, respectively, 79.6%, 55.3%, 16.7% and 1.2%. A large majority of users had more than 5 contacts during the first year: from 84.5% for aflibercept to 55.8% of bevacizumab. Switching during the first 3 injections was relatively common in dexamethasone users: 15.7% of the total user population; 9.7% of aflibercept users switched after the 3rd injection.

Number of injections and between-injections interval (Table 3)

Users with at least 3 injections and neither swiching nor binocularity were 156 for aflibercept, 1,293 for ranibizumab, 396 for bevacizumab, 8 for dexamethasone and 9 for pegaptanib. Both dexamethasone and pegaptanib users were excluded from the analysis.

In this cohort, the mean number of injections was 4.0 for aflibercept, 3.9 for ranibizumab and 3.6 for bevacizumab. Mean interval between injections was 55.7 days for aflibercept, 52.5 days for ranibizumab and 62.7 days for bevacizumab. Patients with persistent follow-up had longer mean interval: respectively, 60.8, 56.0 and 67.6 days for aflibercept, ranibizumab and bevacizumab users.

The temporal trend of the mean interval in the larger subgroup of patients with at least 5 contacts is also represented in Figure 1, as well as this same trend in the smaller subgroup of those having no evidence of diabetes-related eye disease and of those with more than 3 injections (in this last subgroup, interval after the 3rd dose was considered). For ranibizumab the interval was slightly increasing from 50.6 days in 2011 to 54.4 in 2014, and a steeper increase was observed in bevacizumab users, from 58.8 to 64.1 days. Users of aflibercept, who could only be observed in 2013 and 2014, had an intermediate value, and in particular 57.0 days in 2014. The subgroup of users with no evidence of diabetes-related eye disease had similar trends with respect to the previous subgroup as far as ranibizumab and bevacizumab are concerned, and slightly longer intervals in the case of aflibercept (58.8 days in 2014). In users with more than 3 injections the interval after the 3rd was pretty similar in aflibercept and bevacizumab users in 2014 (respectively, 70.5 and 70.3 days), while in ranibizumab users it decreased in 2013 and 2014 to up to 5 days less with respect to bevacizumab and aflibercept users.

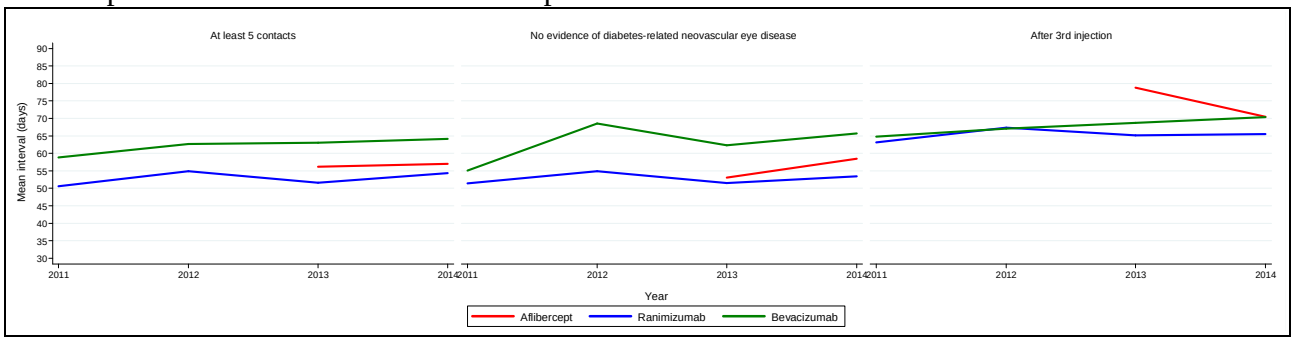

Figure 1. Trend of mean interval between consecutive injections during the first year of follow-up, in days, 2011-2014. The subgroup where interval was computed after the 3rd injection is composed by users with more than 3 injections.

DISCUSSION

The characteristics of 86% of the incident users of intravitreal injections between 2011 and 2015 could be explored in this study, and the pattern of drug use in the first year of treatment between 2011 and 2014 could be described in around 40% of users. Ranibizumab users had an average between-injections interval in the study period of almost two months, and users with a complete loading cycle of 3 injections had an average of 4 injections, with an average interval between consecutive injections of almost two months after the first 3. Bevacizumab was very often used as a single injection. Aflibercept was mostly used in one hospital and for patients with age-related, rather than diabetes-related, eye disease. Aflibercept users had a between-injection interval similar or slightly longer to ranibizumab users.

Users characteristics

Users of aflibercept being older and less often linked to a diabetes-related eye disease is coherent with the approved indications for this drug in Italy.
Socio-economic factors could not be collected for the whole cohort, but appear to be quite evenly distributed across drug exposure strata.

Pattern of use

Ranibizumab and aflibercept were the two most commonly employed anti-VEGF agents in year 2015 in the cohort of users that we could link to a drug (around 50% of users). Users of aflibercept were given the first 3 doses during the first 90 days of follow-up in nearly 80% of cases, while this occurred for only 55% of ranibizumab users (Table 2). Since the approved dosage over the initial period is the same for these two agents (three injections in 60 days), one controversy is to explain the reasons underlying this difference; one can postulate that the hospitals where aflibercept had a large use had a more pronounced tendency to comply with approved dosages, and this may be explored in further studies. On the other hand, the mean number of injections over the first year of follow-up in those with at least 3 injections was similar between users of aflibercept and ranibizumab (4.0 vs 3.9, respectively; see Table 2); this suggests that clinicians don't observe a massive difference in efficacy between the two drugs.
As regards to bevacizumab, the high percentage of users who received a single injection may be explained with the low cost of this drug, which may have been used to explore a possible efficacy of intravitreal injections: this would imply that a high proportion of potential users have low benefit. This data deserves further elaboration.
Most dexamethasone users received a single implant, and if a second procedure was performed, it took place with a different drug. This finding reflects the dosing scheme (every 6 months) approved for this treatment, but on the other hand indicates that Tuscan ophthalmologists were reluctant to employ repeated administrations of dexamethasone

Limitations

Almost 13% of incident users could not be linked to the Inhabitant Registry. This may be due partly to access to Tuscan facilities from other regions, but errors in record linkage cannot be ruled out.

We didn't take into account that patients may have been admitted to hospital during the year of follow-up, and have received there their injection, which would have gone undetected by our analysis. This may have led to a small underestimation of the mean number of injections per patient.

Binocularity could have been underestimated due to our restrictive criteria (interval between injections below 25 days or at least or 3 injections in 55 days). This could have led to overestimate overall intensity of use. On the other hand, more patients could have been labelled as having received a loading dose if the interval between three bilateral injections was about 30 days, or only slightly more, in three months (e.g. right-left-right eye in 60 days). Such patients would receive fewer injections after these three since they would in fact be already in a maintenance phase of chronic or recurrent disease.

The comparison between patterns of use of aflibercept and other drugs may have been influenced by the fact that aflibercept was almost exclusively used in the UH Firenze in the study period.

Ophthalmic contacts may have taken place outside of the reimbursement schema of the healthcare system and be therefore not recorded in the ARS database, especially in higher socio-economic strata of the population. However there is no evidence of difference in the socio-economic

condition of the users of the different drugs, and ophthalmic encounters were recorded in a vast majority of the cohort.

We were not able to observe the clinical outcome of the treatment.

We were not able to compare use of the different drugs after the first year of follow-up. Longer follow-up is needed to do so.

CONCLUSION

Pattern of use of aflibercept and ranibizumab during the first year of utilization were similar in the Tuscan population during the study period. Bevacizumab was often used for one or two injections only. Longer follow-up will allow to compare the drugs in the second and third follow-up year. Access to medical records may allow to investigate comparative efficacy.

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Annex 1. Relevant codes

From DDRUG[2]

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

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

Optical coherence tomography

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

Other contacts

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

[2] 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 associated the dispensing with a specific intravitreal injection.

PP0850 CV FOTOCOAGULAZIONE PANRETINICA comprensiva dell'intero trattamento con minimo di tre sedute 14.24.1

138200 CV FOTOGRAFIA DEL FONDO O SEGMENTO ANTERIORE 95.11.1

Box 1. Flow chart of the study population

INJECTIONS 2011-2015

N of injections 2011-2015: 58,198

N (%) linked to IR: 50,564 (86,9)

N (%) linked to a drug: 36,399(62,5)

USERS 2011-2015

N of prevalent users in 2011-2015: 16,617

INCIDENT USERS 2011-2015

N incident users of injections in 2011-2015: 13,267

N (%) of incident users linked to IR: 11,556 (87.1)

N (%) of incident users with at least 365 days of look-back: **11,377** (85.8)

INCIDENT USERS 2011-2014

N of incident users of injections in 2011-2014: 10,041

N (%) of persons in inhabitant registry, resident in Tuscany: 8,643 (86.1)

N (%) of persons with at least 365 days of look-back: 8,512 (84.8)

N (%) of persons with at least 365 days of follow-up: **8,295** (82.6)

N (%) of persons with at least some injections linked to a drug dispensing: 5,182 (51.6)

N (%) of persons with all injections linked to a drug dispensing: **4,074** (40.6)

Table 1. Incident users 2011-2015: characteristics at first injection

		Aflibercept	Ranibizumab	Bevacizumab	Dexamethasone	Pegaptanib	MISSING
N		587	3,490	1,885	497	51	4,867
F (%)		57.6	55.8	54.0	46.3	45.1	54.3
Mean age		76.9	73.3	70.1	69.9	78.7	72.9
Age band (%)	0-44	0.5	1.8	5.0	5.0	2.0	2.2
	45-54	3.1	4.9	7.6	6.0		5.3
	55-64	5.3	12.3	15.2	17.5	2.0	13.4
	65-74	24.2	28.3	29.9	31.0	21.6	27.3
	75-84	47.5	39.5	32.6	31.6	51.0	38.4
	85+	19.4	13.2	9.7	8.9	23.5	13.4
Citizenship (%)	Italian	24.0	23.2	23.3	24.9	17.6	21.2
	Other		0.3	0.4	0.4		0.3
	Unknown	76.0	76.5	76.3	74.6	82.4	78.5
Education (%)	None or	25.6	27.3	27.2	23.3	43.1	30.0
	Middle school	16.2	17.2	20.2	19.9	17.6	17.9
	High school	10.1	10.3	15.2	14.3	17.6	10.8
	College or	3.2	3.8	4.7	4.0	3.9	3.3
	Unknown	45.0	41.4	32.7	38.4	17.6	37.9
Proxy of diabetes – related eye disease (%)	Diabetes	15.0	28.6	31.4	23.3	25.5	31.8
	Argon	3.1	14.9	21.1	14.9	5.9	16.4
	Younger than 55 at first injection	3.6	6.7	12.6	11.1	2.0	7.5
	Any proxy among the previous	20.3	37.2	45.7	40.2	33.3	41.6
Glaucoma		6.0	4.8	5.1	3.8	3.9	4.0
Utilization of drugs during the previous 365 days (%)	Antihypertensives	63.9	65.2	61.4	57.3	78.4	65.2
	Statins	69.7	70.9	66.2	63.8	84.3	70.2
	Antithrombotics	73.3	74.7	69.5	70.6	90.2	75.3
Utilization of ophthalmic services during the previous 365 days (%)	Specialist	85.5	81.1	82.7	82.5	90.2	80.0
	OCT	48.9	46.6	44.7	48.1	56.9	47.0
	Fluorescence imaging with indocyanine	9.9	7.1	5.5	4.2	0.0	3.4
	Chorioretina	67.5	62.5	52.3	56.5	66.7	63.5
Year of first injection (%)	2011		11.1	32.0		21.6	25.9
	2012		12.6	19.4	9.7	29.4	19.6
	2013	4.6	25.4	17.2	21.9	9.8	14.5

	2014	35.4	23.1	17.5	24.1	3.9	18.6
	2015	60.0	27.9	13.9	44.3	35.3	21.4
Years of follow-up (%)	0	60.5	29.5	16.3	45.9	37.3	23.5
	1	35.3	23.8	18.6	23.9	11.8	20.3
	2	4.3	24.8	17.5	21.5	13.7	15.4
	3		21.8	47.6	8.7	37.3	40.9
Hospital (%)	LHU 1 Massa	0.2	1.0		1.6		3.0
	LHU 2 Lucca						7.9
	LHU 3 Pistoia		0.1	0.1			15.7
	LHU 4 Prato						8.4
	LHU 5 Pisa	0.9	1.9	2.8		15.7	1.9
	LHU 6 Livorno		0.0	6.7			11.9
	LHU 7 Siena						0.2
	LHU 8 Arezzo			0.2			16.2
	LHU 10		1.1				4.0
	LHU 11 Empoli		11.1	5.4	6.2	2.0	1.5
	LHU 12	1.7	3.3	1.4	0.4		10.4
	UH Pisa	11.8	22.8	30.1	38.6	2.0	1.8
	UH Siena	7.8	24.0	25.8	20.9	23.5	0.5
	UH Firenze	77.7	34.6	27.5	32.2	56.9	16.4

Table 2. Incident users 2011-2014, with at least one year of follow-up and all injections linked to a drug: characteristics at baseline and follow-up.

		Aflibercept	Ranibizumab	Bevacizumab	Dexamethasone	Pegaptanib
N		226	2160	1404	255	29
F (%)		58.8	57.7	54.5	48.6	37.9
Mean age		77.9	73.4	69.6	70.0	77.4
Age band (%)	0-44	0.4	1.9	5.1	5.1	3.4
	45-54	0.9	4.4	8.0	5.5	
	55-64	3.5	12.1	15.4	18.0	3.4
	65-74	25.7	29.4	31.4	30.6	24.1
	75-84	48.2	39.6	31.3	31.0	48.3
	85+	21.2	12.7	8.8	9.8	20.7
Citizenship (%)	Italian	21.2	23.5	24.1	24.7	17.2
	Other		0.4	0.1		
	Unknown	78.8	76.2	75.8	75.3	82.8
Education (%)	None or primary	24.3	27.7	26.3	24.7	34.5
	Middle school	15.5	16.8	20.4	20.0	24.1
	High school	9.3	10.8	15.2	14.9	20.7
	College or higher	2.7	3.4	4.7	4.3	6.9
	Unknown	48.2	41.3	33.4	36.1	13.8
Proxy of diabetes-related eye disease (%)	Diabetes	15.5	28.9	32.0	20.4	20.7
	Argon	3.1	15.3	22.0	13.3	6.9
	Younger than 55	1.3	6.3	13.2	10.6	3.4
	Any proxy among the previous	18.6	37.6	47.1	38.0	31.0
Glaucoma (%)		6.2	5.4	4.7	4.3	0.0
Utilization of drugs during the previous 365 days (%)	Antihypertensives	65.5	66.9	61.5	59.2	79.3
	Statins	71.2	72.2	66.1	65.5	86.2
	Antithrombotics	75.2	76.2	69.5	72.9	89.7
Utilization of ophthalmic services during the previous 365 days (%)	Specialist	91.6	81.7	81.8	86.7	86.2
	OCT	44.2	46.8	44.0	50.6	44.8
	Fluorescence imaging with indocyanine	7.5	8.3	5.7	3.5	0.0
	Chorioretina	70.8	65.0	52.6	61.2	69.0
Year of first injection (%)	2011		12.5	36.5		31.0
	2012		17.1	21.6	17.6	44.8
	2013	11.1	37.7	21.3	38.0	17.2
	2014	88.9	32.7	20.7	44.3	6.9

Years of follow-up (%)	1	89.8	34.8	22.9	45.1	20.7
	2	10.2	37.2	21.9	38.8	24.1
	3		28.0	55.2	16.1	55.2
Hospital of first injection (%)	LHU 1 Massa		1.4		1.6	
	LHU 3 Pistoia		0.1	0.1		
	LHU 5 Pisa		1.1	3.3		
	LHU 6 Livorno			2.5		
	LHU 8 Arezzo			0.2		
	LHU 11 Empoli		10.6	4.1	6.7	
	LHU 12 Viareggio		2.6	1.2		
	UH Pisa	1.3	22.4	33.7	36.1	
	UH Siena	3.1	27.0	31.3	24.7	34.5
	UH Firenze	95.6	34.7	23.7	31.0	65.5
Possible binocularity during the first year (%)		5.8	5.6	7.3	0.8	0.0
Number of injections during the first year of follow-up (%)	1	9.7	17.7	40.7	57.6	13.8
	2	3.1	10.1	18.9	25.5	31.0
	3	35.4	39.2	23.1	8.2	27.6
	4	18.6	10.2	6.9	4.7	10.3
	5	17.7	7.4	3.8	2.4	6.9
	6	8.0	9.8	2.6	1.6	6.9
	7	5.3	2.4	0.9		
	8	0.4	0.8	0.6		3.4
	9		0.6			
	10		0.1	0.1		
	12+	1.8	1.7	2.4		
Number of contacts during the first year of follow-up (%)	1	2.7	4.7	10.5	9.4	
	2	2.2	4.8	8.8	11.0	6.9
	3	4.0	7.1	11.6	7.1	3.4
	4	4.9	7.0	11.0	3.9	3.4
	5	7.5	8.8	8.3	8.6	13.8
	6	8.8	8.7	8.3	7.8	13.8
	7	7.1	8.1	6.6	11.4	10.3
	8	10.6	8.5	7.8	11.0	10.3
	9	12.4	6.4	5.0	7.8	6.9
	10	11.1	7.3	4.1	3.1	6.9
	11	8.0	5.7	4.3	5.5	13.8
	12+	20.8	22.9	13.7	13.3	10.3
First 3 doses in 90 days (%)		79.6	55.3	16.7	1.2	6.9
Intensive	At least 5 contacts	84.5	74.7	55.8	68.6	86.2

	Persistent follow-up (less than 90 days between contacts)	46.5	24.5	16.5	23.1	27.6
Switching during the first year (%)	During the first 3 injections	5.8	3.5	7.8	15.7	17.2
	After the first 3 injections	9.7	6.4	3.2	0.4	6.9

Table 3. Mean number of injections and mean interval between injections in incident users 2011-2014, with at least a year of follow-up, at least 3 injections, no suspect binocularity and no switching, and in subgroups. In the subgroup of users of at least 4 injections the mean interval is computed starting from the 3rd injection. IQ: interquartile range.

Subgroup	Measure	Year of first injection	Aflibercept	Ranibizumab	Bevacizumab
All	N	All years	156	1293	396
	Mean number of injections (IQ range)		4.0 (3-5)	3.9 (3-5)	3.6 (3-4)
	Mean interval in days (SD)		55.7 (22.6)	52.5 (26.1)	62.7 (32.3)
Users with persistent follow-up	N	All years	82	367	98
	Mean number of injections (IQ range)		4.4 (3-5)	4.9 (3-6)	4.4 (3-5)
	Mean interval in days (SD)		60.8 (19.9)	56.0 (21.6)	67.6 (30.4)
Users with at least 5 contacts	N	All years	146	1136	313
	Mean number of injections (IQ range)		4.1 (3-5)	4.0 (3-5)	3.7 (3-4)
	Mean interval in days (SD)		56.9 (22.7)	52.9 (25.7)	61.7 (30.8)
	N	2011		178	112
		2012		228	59
		2013	16	396	70
		2014	130	334	72
	Mean number of injections (IQ range)	2011		3.9 (3-5)	3.6 (3-4)
		2012		4.1 (3-5)	3.4 (3-3)
		2013	3.7 (3-4)	3.9 (3-5)	3.6 (3-4)
		2014	4.1 (3-5)	4.1 (3-5)	4.0 (3-5)
	Mean interval in days (SD)	2011		50.6 (22.9)	58.8 (32.2)
		2012		54.9 (26.8)	62.7 (34.0)
		2013	56.1 (24.8)	51.5 (25.8)	63.0 (26.6)

		2014	57.0 (22.5)	54.4 (26.1)	64.1 (29.9)
Users with no evidence of diabetes-related eye disease	N	All years	123	716	177
	Mean number of injections (IQ range)		4.1 (3-5)	4.0 (3-5)	3.7 (3-4)
	Mean interval in days (SD)		57.8 (22.6)	52.8 (25.1)	61.8 (31.1)
	N	2011		140	61
		2012		177	31
		2013	15	232	35
		2014	108	167	50
	Mean number of injections (IQ range)	2011		3.9 (3-5)	3.5 (3-4)
		2012		4.1 (3-5)	3.2 (3-3)
		2013	3.7 (3-4)	3.9 (3-5)	3.9 (3-5)
		2014	4.2 (3-5)	4.0 (3-5)	4.1 (3-5)
	Mean interval in days (SD)	2011		51.4 (24.1)	55.0 (29.4)
		2012		54.9 (26.7)	68.6 (37.1)
		2013	53.0 (22.3)	51.5 (25.2)	62.3 (26.3)
		2014	58.4 (22.6)	53.4 (24.3)	65.6 (31.5)
Users with at least 4 injections and 5 contacts	N	All years	84	484	106
	Mean number of injections (IQ range)		4.9 (4-5)	5.3 (4-6)	5.0 (4-6)
	Mean interval in days after the 3rd injection (SD)		71.3 (15.8)	65.5 (20.7)	67.8 (21.3)
	N	2011		73	35
		2012		109	12
		2013	8	152	23
		2014	76	150	36
	Mean number of injections (IQ range)	2011		5.2 (4-6)	5.0 (4-6)
		2012		5.2 (4-6)	5.0 (4-6)

		2013	4.4 (4-5)	5.4 (4-6)	5.0 (4-5)
		2014	4.9 (4-5)	5.5 (5-6)	5.1 (4-6)
	Mean interval in days after the 3rd injection (SD)	2011		63.1 (15.5)	64.8 (23.2)
		2012		67.3 (21.5)	67.0 (19.8)
		2013	78.8 (10.0)	65.1 (21.2)	68.7 (17.9)
		2014	70.5 (16.2)	65.6 (21.7)	70.3 (22.2)