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Title

Diffusion of anti-VEGF Injections in a National Health System

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Contribution statement

APM, AFM, RS conceived and designed the study, collected and analysed the data and drafted the manuscript. PA advised on the statistical analysis and on the presentation of results. ARS participated in the design of the study, on the discussion and provided the clinical critical feedback. JP advised on the analysis and presentation of results, and provided critical feedback to the manuscript. All the authors revised the manuscript for important intellectual content, contributed to the data interpretation, and writing and critically reviewing of the manuscript at all stages, and approved the final copy.

Strengths and limitations of the study

Strengths

- A unique analysis of temporal and geographical patterns of the diffusion of anti-VEGF treatments for eye diseases during one decade in a National Health System
- The analysis includes all public hospitals for a period of 1 decade
- Results will raise awareness to inequalities in access to eye care that can be leading some patients to lose vision due to treatable conditions
- The study points some determinants that can be modified to ensure that all patients with progressive eye conditions are treated equally

Limitations

- The lack of specific codes for anti-VEGF injections
- The exclusion of the activity in the private health sector
- Absence of individual data

Abstract

Purpose

To analyse the temporal and geographical diffusion of anti-VEGF interventions and its determinants in a National Health Service (NHS).

Design

Observational ecological retrospective database study

Setting

NHS Portuguese Hospitals

Participants

All in-patient and day cases related to eye diseases at all Portuguese public hospitals for the period 2002-2012 were selected on the basis of four International Classification of Diseases 9th revision, Clinical Modification (ICD-9-CM) codes for procedures: 1414, 1475, 1479, 149.

Primary and secondary outcome measures

We measured anti-VEGF treatment rates by year and county. The determinants of the geographical diffusion were investigated using generalized linear modelling.

Results

We analysed all hospital discharges from all NHS hospitals in Portugal (98,408 hospital discharges corresponding to 57,984 patients). National rates of hospitals episodes for the codes for procedures used were low before anti-VEGF approval in 2007 (less than 12% of hospital discharges). Between 2007 and 2012, the rates of hospital episodes related to the introduction of anti-VEGF injections increased by 27% per year. Patients from areas without ophthalmology departments received fewer treatments than those from areas with ophthalmology departments. The availability of an ophthalmology department in the county increased the rates of hospital episodes, by 243% and a 100-persons greater density per square kilometre raised the rates by 11%.

Conclusions

Our study shows a large but unequal diffusion of anti-VEGF treatments, despite the universal coverage and very low co-payments. The technological innovation in ophthalmology may thus produce unexpected inequalities, related to financial constraints, unless the implementation of innovative techniques is planned and regulated.

Introduction

Age Related Macular Degeneration (AMD) is a chronic, progressive disease and the most common cause of visual impairment in developed countries in patients older than 65 years.[1-7] AMD requires lifelong observation and interventions.[8] AMD can be divided into two stages: early AMD, characterized by sub-retinal pigmented epithelium deposits (drusen) and pigmentary changes, and advanced AMD.[5] Advanced AMD has atrophic and neovascular forms. Although neovascular AMD comprises only 10% of the burden of the disease, it is responsible for 90% of severe vision loss.[1, 9-12] Vision loss leads to reduced quality of life and autonomy and is associated with large costs for health systems and the society.[10, 13-15]

Before the introduction of antivascular endothelial growth factor (anti-VEGF) treatments, AMD was largely untreatable.[16] Anti-VEGF therapy for neovascular AMD has substantially changed the management of the disease.[16, 17]These drugs are injected into the vitreous chamber to reduce neovascular formation in the macula.[2] Currently the most common anti-VEGF therapies in Portugal are: i) Ranibizumab (Lucentis, Novartis), licensed for the treatment of neovascular AMD by the Food and Drug Administration (FDA) in 2006 and by the European Medicines Agency (EMA) in 2007. In Portugal ranibizumab has been covered by the National Health Service (NHS) since 2008. Ranibizumab is the most widely used approved anti-VEGF drug in Europe;[1, 3, 18] ii) Bevacizumab (Avastin, Roche) was licensed in 2004 by the FDA, and by EMA in 2005 for the treatment of metastatic colorectal cancer. It has been widely used for the treatment of neovascular AMD as an off-label alternative;[16] iii) Pegaptanib sodium (Macugen, Eyetech/Pfizer) was approved by FDA 2004, and by EMA in 2006 for the treatment of neovascular AMD. It is less commonly used in clinical practice as it is not as effective as ranibizumab or bevacizumab.[2, 19] In Portugal this therapy was approved but not marketed; iv) Aflibercept (Eylea, Bayer) was approved for wet AMD treatment by FDA in

2011 and by the EMA in 2012. In Portugal aflibercept has been covered by the NHS since 2014.

Several clinical trials have shown that intravitreal injections prevent vision loss in the majority of patients and, in some cases, significantly improve vision [16, 20-22] with low numbers of serious adverse effects.[8] Subsequently, anti-VEGF therapy has become the standard clinical option to treat AMD patients.[18, 20, 21] In 2011, anti-VEGF therapy was also introduced as treatment for diabetic macular oedema and central retinal vein occlusion.[1, 18, 23]

New therapies such as anti-VEGF injections improve the clinical course of diseases but represent substantial expenditures for healthcare systems. [24] In a context of economic recession and tight public budgets the introduction and diffusion of these treatments can face substantial barriers.[25] Despite the strong equity commitment of the Portuguese NHS, one of the expected barriers is likely to be geographical due to unequal distribution of resources across areas.

The aim of this study was to examine the diffusion of anti-VEGF drugs in the Portuguese NHS by analysing the temporal and geographical diffusion patterns and its determinants. We conducted a longitudinal study in order to measure the evolution of hospital episodes related to anti-VEGF treatments per county from 2002 to 2012.

Methods

Data sources and extraction strategies

We used an administrative database that includes demographic, administrative and clinical information from all in-patient and day case episodes performed at all Portuguese NHS hospitals during the years 2002 to 2012. Authorization to use these information was obtained from Institutional Review Board (IRB) from Escola Nacional de Saúde Pública/Universidade Nova de Lisboa. In order to select the episodes related to intravitreal injections for anti-VEGF treatments,

we used the following International Classification of Diseases 9th revision, Clinical Modification (ICD-9-CM) codes for procedures: 1414, 1475, 1479, 149. These codes have been commonly used in the literature but they are likely to capture other treatments such as injectable antibiotic or corticosteroids.[1] Effects to our estimation caused by the poor specificity of the code were reduced using two methods: first, years 2002-2006 were included as baseline as before 2006 intravitreal anti-VEGF treatments for ophthalmologic use were not licensed; second, we crossed information of age with principal diagnosis. We considered that AMD only affects people over 55[26] and anti-VEGF are used for specific diagnosis, such as AMD or diabetic macular oedema. Cases in which diagnosis and/or age were not likely to require anti-VEGF treatment were excluded from analysis. Baseline years provide the picture of the number of cases associated with the codes but not related with anti-VEGF treatments.

We used the indicators bellow:

- The absolute values of the number of hospital episodes per year. Episodes were then disaggregated by: i) sex, ii) age of the patients (under/over 60 years old), iii) principal diagnosis.
- The number of patient treated per year. To calculate the number of patients, we considered one treatment per person per year, regardless of the number of episodes of care (number of treatments) that occurred in each year.
- The yearly rates of hospital episodes per 100,000 population [(number of episodes per year/annual average resident population per year) x 100,000].
- The age-standardized rates of hospital episodes per 100,000 population by counties per year [(number of episodes by county and year/annual average resident population per county and year)x 100,000] using general demographic information published by Statistics Portugal.[27] We used the direct method of standardization as described by Beaghole and collegues with standard Portuguese population.[28] The age-standardisation was necessary to control the effect of age heterogeneity across populations living in different counties.

Study analysis

We first evaluated the diffusion of treatments across areas, using the mean, minimum and maximum values of the rates of hospital episodes per 100,000 population in 2002, 2006 and 2012. The relative variation coefficient was used to measure the dispersion of the diffusion.

Three time points were selected because they corresponded to: 2002 – the first year included in this study, 2006- the year before the approval of intravitreal injections with anti-VEGF by EMA and 2012 because it was the latest available information when this study started.

To investigate the determinants of geographical diffusion of anti-VEGF treatments we used generalized linear modelling. Considering the longitudinal nature of the data and its non-normal distribution we used Generalized Estimating Equations (GEE).[29] The dependent variable was defined as the yearly rate of hospital episodes per county per 100,000 population. We defined as independent variables: i) the years during which the geographical diffusion was analysed (a linear trend); ii) a dichotomous variable to indicate the year where the drug was authorized in the EU by EMA (Anti-VEGF therapy availability: 0-not available; 1–available; iii) a dichotomous variable to indicate the availability of an ophthalmology department in the hospital of the patients' county of residence (Ophthalmology department availability: 0-no ophthalmology department; 1–ophthalmology department) and iv) population density (population per squared kilometre) in the county. The model was defined as gamma log link distribution regression model as the rate was expected to be positively skewed with an autoregressive first order matrix representing time dependence within repeated subject.[30] A total of 278 counties were considered as "subjects" with repeated measures. Year and dichotomous variable "anti-VEGF availability" were defined as within subject independent variables. Dichotomous variable "Ophthalmology department availability" and "population density rates" were defined as between subject variables. The analysis was performed using IBM SPSS Statistics 21.0.

Results

The final sample included 98,408 hospital episodes. Figure 1 shows that the total number of episodes increased from 1,815 in 2002 to 25,106 in 2012. This corresponds to a mean annual increase of 32%.

===== FIGURE 1 =====

In 2012, the number of treated patients was six times higher than in 2002, corresponding to a mean annual increase of 24%. The ratio number episodes/number patients was 1.16 in 2002, 1.17 in 2006 and 2.1 in 2012. The most relevant demographic information was the percentage of patients treated who were older than 60 years of age. The figures changed from about 60% in 2002 to 80% in 2012.

Figure 2 shows the five principal diagnoses responsible for the episodes detected. The figure is expected to provide a picture of the growth of the number of episodes per year and number of patients treated per diagnoses. The most common diagnosis was exudative age -related macular degeneration, followed by diabetic macular oedema (diabetes with ophthalmic complications), oedema of the retina, retinal neovascularization, and non-specific AMD. The cumulative percentage of episodes associated with these five diagnoses was 73% in 2012, in contrast with only 16% in 2002. These values corresponded to an increase in the yearly rates of hospital episodes per 100,000 individuals from 17.4 in 2002 to 238.77 in 2012.

===== FIGURE 2 =====

Table 1 gives a summary of the mean, minimum and maximum values in 3 specific years of the rates of hospital episodes per 100,000 population. Both maximum and minimum rate values increased over time. The relative variation coefficient varied from 200% in 2002, to 204% in 2006, and 209% in 2012. The relative coefficient of variation indicates that rates per county have a great dispersion and that this dispersion did not reduce over time. The first quintile always contains rates equal to zero, which means that there are counties without events. In 2002 there were 58 counties in the first quintile (without

episodes). The number of counties without episodes reduced over time to 33 in 2006 and 3 in 2012. All the mean values per quintile rose in the period analysed.

===== TABLE 1 =====

Results of the regression analysis are summarized in Table 2. In agreement with the initial prediction and consistent with the introduction of the new treatment with anti-VEGF, the model shows a significant effect of the variable "year", $p<0.0001$. For each additional year the rate of hospital episodes increased by 28%. The rate was significantly higher after the EMA approval, in Table 2 results for "Anti-VEGF therapy availability", $p<0.0001$. With the approval of this treatment the rates of hospital episodes increased by 27%. The availability of an ophthalmology department in the hospital of the county (in Table 2 results for "Ophthalmology department availability") significantly increased the rates of hospital episodes by 243%, $p<0.0001$ (compared with counties without). The positive association between the variable "Ophthalmology department availability" and our dependent variable indicates that anti-VEGF treatments were more frequent to patients living near hospitals with ophthalmology departments, which are typically located in areas of median/high population density. There was a positive association between the dependent variable and population density. An increase of 100 persons per square kilometre raised the rates of hospital episodes by 11%. This results show that patients living in rural areas were less frequently treated.

===== TABLE 2 =====

Discussion

With this study we wanted to investigate the diffusion of anti-VEGF treatments for eye disease in Portugal looking for possible determinates and/or barriers. We performed this investigation by characterizing the temporal and geographical distribution of anti-VEGF treatments using codes for specific type of procedures from all episodes performed in public hospitals. Our results show that the number of episodes for the codes analysed was low before the

introduction of anti-VEGF treatments. The numbers episodes rose significantly since the treatment was introduced in the country in 2007. The most relevant finding was that patients from small areas without ophthalmology departments near their residence received fewer treatments as revealed by the geographical distribution of episodes. The unequal distribution is puzzling, given the equity-oriented nature of the Portuguese NHS

We consider three possible barriers for the equitable anti-VEGF diffusion related to legal, technical and financial factors. Following the EMA approval of this treatment in 2007 and the NHS coverage decision in 2008 the treatment became legally available at all ophthalmology departments in Portugal. One can thus say that the legal problem was sorted. However technical conditions were imposed for the use of this treatment that included extra training for doctors and that the procedure needed to be performed in the operation theatre.[18] These technical requirements possibly created financial and service capacity pressures on ophthalmology departments.[1, 4] Indeed, higher rates of treatment were observed mostly in areas around big cities and specialized centres. Smaller hospitals may have taken longer to adopt this treatment due to budget limitations or technical conditions.

Regarding financial barriers we can speculate about two main budget limitations that reduced the speed of diffusion of anti-VEGF treatments. The first financial challenge is the cost of the treatment of approximately €1,913 per episode, a figure similar to the United Stats.[25, 31] In Portugal, hospitals receive a global budget from the government that covers the cost of all drugs and medical devices.[18] During the period included in this study the financing methodology used to allocate resources to the Portuguese NHS hospitals has been subject to several changes. This included the introduction of different unit payment and new incentive programs that rely on quality and cost indicators. These changes to hospital budgets and pressure for cost-containment may have reduced the availability of anti-VEGF treatments in small hospitals concentrating patients in big centres with limited capacity. A second financial barrier for hospitals is the fact that the intravitreal injections need to be administered in an operating room by an ophthalmologist. Typically, patients receive three injections in the first 3 months, followed by monthly visits for assessment and further injections as

necessary.[22] These surgical procedures and monthly appointments impose high demands on hospitals (staff and facilities). In a period of tight budgets, expansions in the medical staff or facilities are difficult to implement, these problems have been recently reported by Marko Hawlina, a retinal specialist form Slovenia, quoting results of a survey of the European Union of Medical Specialists.[32] Thus, some hospitals may have delayed the start of these treatments or they may still not be available.

The reasons outlined above have implications for the geographical diffusion of the treatment leading to inequalities. Patients referred from distant cities or rural areas may have delayed access to treatments. The lower rate of treatments in patients living in areas of low population density may also indicate that these patients are more likely to miss follow-up appointments. Travelling distances may be a barrier to attending appointments as reported by other studies.[33-35] This evidence is a cause of concern because vision loss due to the spectrum of diseases for which anti-VEGF treatments are indicated cannot be restored. This may lead to an increased number of people becoming visually impaired due to treatable causes.

During this study we found some limitations: the lack of specific codes for anti-VEGF injections, the exclusion of the activity in the private sector and the absence of individual data. Limitations caused by non-specific codes have been described in methods. Numbers from private treatments were likely to be small because this treatment is expensive and patients tend to look for care in the national health system where treatment is free. The lack of individual data limited our analysis of socio-economic determinants such as patient income or education level or other clinical conditions that could restrict the prescription of anti-VEGF therapy. However, with the available data we were able to construct a complex and multivariable model to explain the geographical diffusion and time variation based on a nationally representative database, with many types of hospital settings and geographic areas that would be difficult to perform with a limited sample number of cases.

In brief, the use of anti-VEGF drugs in ophthalmology marked the beginning of effective treatments for age related eye diseases that can lead to severe visual

impairment. This study shows that the number of intravitreal procedures increased substantially since anti-VEGF treatments were approved in Portugal but that the diffusion was inequitably distributed. Local restrictions to the temporal and geographical diffusion seem mostly imposed by financial aspects. These financial constraints may arise, not only, from cuts in budgets in the health care system but also from difficulties for families to fund travel costs. With the aging of the population and the expected growth in conditions such as diabetic retinopathy and age-related macular degeneration, the demand for these treatments is likely to increase.[7] The combination of these factors will maintain pressure on ophthalmology departments delivering eye care. Health authorities need to consider the equitable distribution when planning human and material resources for ophthalmology departments.

Table 1: Age-standardized rates of hospital episodes per 100.000 populations per county in the year 2002, 2006 and 2012. Values show quintiles mean, minimum and maximum values.

Quintile	2002			2006			2012		
	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
1st	0	0	0	0.0001	0	0.0002	0.0013	0	0.0024
2nd	0.0002	0.0001	0.0003	0.0003	0.0002	0.0005	0.0037	0.0024	0.0051
3rd	0.0005	0.0004	0.0008	0.0009	0.0006	0.0013	0.0069	0.0051	0.0091
4th	0.0012	0.0008	0.0017	0.0019	0.0013	0.0026	0.0148	0.0093	0.0221
5th	0.0048	0.0017	0.0231	0.008	0.0026	0.0459	0.0764	0.0222	0.3745
Total	0.0013	0	0.0231	0.0022	0	0.0459	0.0208	0	0.3745

Ratio **Wald chi-square test of significance (95% Confidence Interval)

Table 2: Results of the Generalized Estimating Equation for the rate of hospital episodes per 100.000 population per year and independent variables were: year, Anti-VEGF therapy availability (separating years before and after the drug was authorized by EMEA); Ophthalmology department availability (representing the availability of ophthalmology departments in the hospitals of county of residence) and population density (population per square kilometre in the county). Total number of counties is 278.

Parameter	**IRR***	**p- value**	**95%CI****	
			Lower	**Upper**
Year (from 2002 to 2012)	1.281	<0.001	1.263	1.299
Anti-VEGF therapy availability (0- not available; 1 – available)	1.270	<0.001	1.183	1.362
Ophthalmology department availability (0 - no ophthalmology dept; 1 –ophthalmology dept)	3.430	<0.001	2.566	4.583
Density rate (per 100 persons)	1.113	<0.001	1.095	1.132

*Incidence Rate Ratio **Wald chi-square test of significance (95% Confidence Interval)

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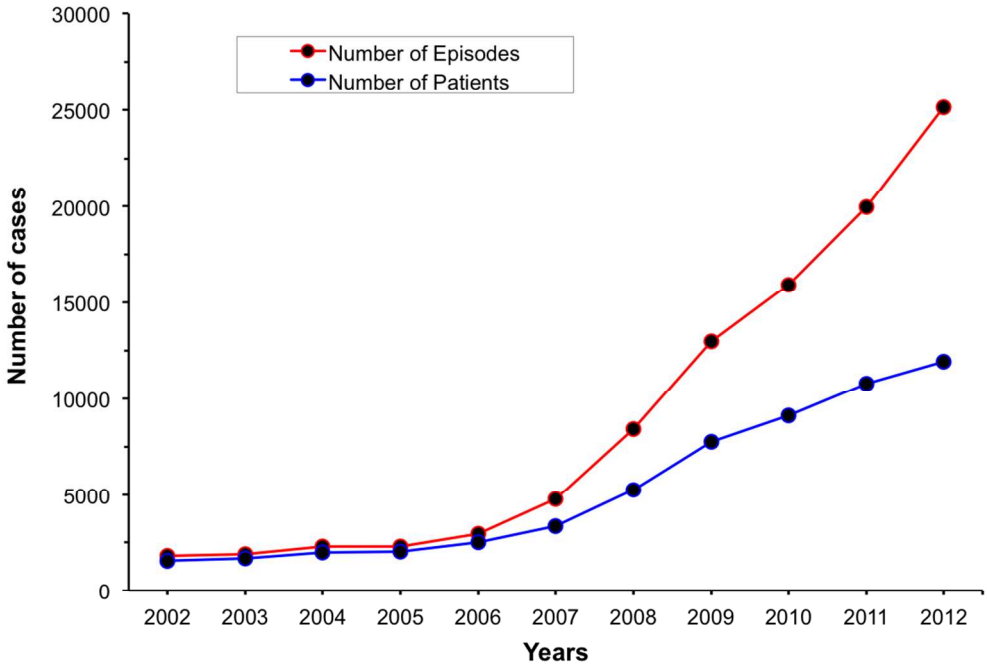
Figure legends

Figure 1

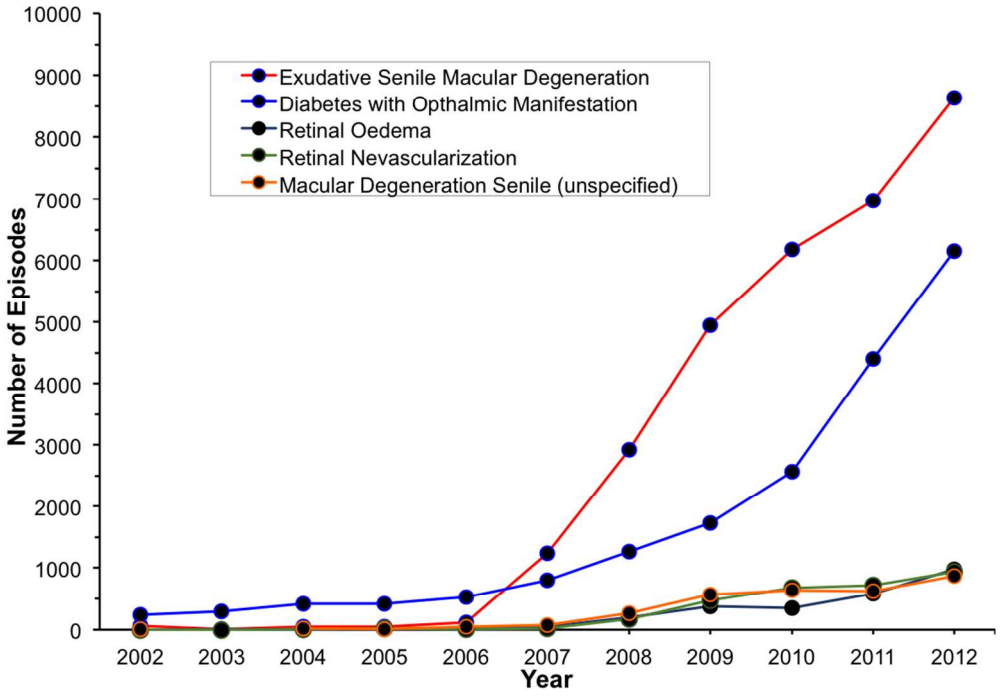
Annual number of hospital episodes of anti-VEGF treatments and annual number of treated patients from 2002 to 2012.

Figure 2

Number of hospital episodes associated with the top 5 diagnoses by year.



Annual number of hospital episodes of anti-VEGF treatments and annual number of treated patients from 2002 to 2012.



Number of hospital episodes associated with the top 5 diagnoses by year

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Title

Diffusion of anti-VEGF Injections in the Portuguese National Health System

Authors

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Contribution statement

APM, AFM, RS conceived and designed the study, collected and analysed the data and drafted the manuscript. PA advised on the statistical analysis and on the presentation of results. ARS participated in the design of the study, on the discussion and provided the clinical critical feedback. JP advised on the analysis and presentation of results, and provided critical feedback to the manuscript. All the authors revised the manuscript for important intellectual content, contributed to the data interpretation, and writing and critically reviewing of the manuscript at all stages, and approved the final copy.

Strengths and limitations of the study

Strengths

- A unique analysis of temporal and geographical patterns of the diffusion of anti-VEGF treatments for eye diseases during one decade in a National Health System
- The analysis includes all public hospitals for a period of 1 decade
- Results will raise awareness to inequalities in access to eye care that can be leading some patients to lose vision due to treatable conditions
- The study points some determinants that can be modified to ensure that all patients with progressive eye conditions are treated equally

Limitations

- The lack of specific codes for anti-VEGF injections
- The exclusion of the activity in the private health sector
- Absence of individual data

Abstract

Objectives

To analyse the temporal and geographical diffusion of anti-VEGF interventions and its determinants in a National Health Service (NHS).

Setting

NHS Portuguese Hospitals

Participants

All in-patient and day cases related to eye diseases at all Portuguese public hospitals for the period 2002-2012 were selected on the basis of four International Classification of Diseases 9th revision, Clinical Modification (ICD-9-CM) codes for procedures: 1414, 1475, 1479, 149.

Primary and secondary outcome measures

We measured anti-VEGF treatment rates by year and county. The determinants of the geographical diffusion were investigated using generalized linear modelling.

Results

We analysed all hospital discharges from all NHS hospitals in Portugal (98,408 hospital discharges corresponding to 57,984 patients). National rates of hospitals episodes for the codes for procedures used were low before anti-VEGF approval in 2007 (less than 12% of hospital discharges). Between 2007 and 2012, the rates of hospital episodes related to the introduction of anti-VEGF injections increased by 27% per year. Patients from areas without ophthalmology departments received fewer treatments than those from areas with ophthalmology departments. The availability of an ophthalmology department in the county increased the rates of hospital episodes, by 243% and a 100-persons greater density per square kilometre raised the rates by 11%.

Conclusions

Our study shows a large but unequal diffusion of anti-VEGF treatments, despite the universal coverage and very low co-payments. The technological innovation in ophthalmology may thus produce unexpected inequalities, related to financial constraints, unless the implementation of innovative techniques is planned and regulated.

Introduction

Age Related Macular Degeneration (AMD) is a chronic, progressive disease and the most common cause of visual impairment in developed countries in patients older than 65 years.(1-7) AMD requires lifelong observation and interventions.(8) AMD can be divided into two stages: early AMD, characterized by sub-retinal pigmented epithelium deposits (drusen) and pigmentary changes, and advanced AMD.(5) Advanced AMD has atrophic and neovascular forms. Although neovascular AMD comprises only 10% of the burden of the disease, it is responsible for 90% of severe vision loss.(1, 9-12) Vision loss leads to reduced quality of life and autonomy and is associated with large costs for health systems and the society.(10, 13-15)

Before the introduction of antivascular endothelial growth factor (anti-VEGF) treatments, AMD was largely untreatable.(16) Anti-VEGF therapy for neovascular AMD has substantially changed the management of the disease.(16, 17)These drugs are injected into the vitreous chamber to reduce neovascular formation in the macula.(2) Currently the most common anti-VEGF therapies in Portugal are: i) Ranibizumab (Lucentis, Novartis), licensed for the treatment of neovascular AMD by the Food and Drug Administration (FDA) in 2006 and by the European Medicines Agency (EMA) in 2007. In Portugal ranibizumab has been covered by the National Health Service (NHS) since 2008. Ranibizumab is the most widely used approved anti-VEGF drug in Europe;(1, 3, 18) ii) Bevacizumab (Avastin, Roche) was licensed in 2004 by the FDA, and by EMA in 2005 for the treatment of metastatic colorectal cancer. It has been widely used for the treatment of neovascular AMD as an off-label alternative;(16) iii) Pegaptanib sodium (Macugen, Eyetech/Pfizer) was approved by FDA 2004, and by EMA in 2006 for the treatment of neovascular AMD. It is less commonly used in clinical practice as it is not as effective as ranibizumab or bevacizumab.(2, 19) In Portugal this therapy was approved but not marketed; iv) Aflibercept (Eylea, Bayer) was approved for wet AMD treatment by FDA in

2011 and by the EMA in 2012. Aflibercept is covered by the Portuguese NHS since 2014.

Several clinical trials have shown that intravitreal injections prevent vision loss in the majority of patients and, in some cases, significantly improve vision (16, 20-22) with low numbers of serious adverse effects.(8) Subsequently, anti-VEGF therapy has become the standard clinical option to treat AMD patients.(18, 20, 21) In 2011, anti-VEGF therapy was also introduced as treatment for diabetic macular oedema and central retinal vein occlusion.(1, 18, 23)

New therapies such as anti-VEGF injections improve the clinical course of diseases but represent substantial expenditures for healthcare systems. (24) To face rising costs of health care co-payment have been introduced during the period of this study in public Portuguese hospitals. If not exempt due special circumstances such as disabled, patients receiving anti-VEGF injections have to pay typically 7.5 euro per appointment with their physician at the hospital. In a context of economic recession and tight public budgets the introduction and diffusion of these treatments can face substantial barriers.(25) Despite the strong equity commitment of the Portuguese NHS, one of the expected barriers is likely to be geographical due to unequal distribution of resources across areas.

The aim of this study was to examine the diffusion of anti-VEGF drugs in the Portuguese NHS by analysing the temporal and geographical diffusion patterns and its determinants. We conducted a longitudinal study in order to measure the evolution of hospital episodes related to anti-VEGF treatments per county from 2002 to 2012.

Methods

Data sources and extraction strategies

We used an administrative database that includes demographic, administrative and clinical information from all in-patient and day case episodes performed at

all Portuguese NHS hospitals during the years 2002 to 2012. Authorization to use these information was obtained from Institutional Review Board (IRB) from Escola Nacional de Saúde Pública/Universidade Nova de Lisboa. In order to select the episodes related to intravitreal injections for anti-VEGF treatments, we used the following International Classification of Diseases 9th revision, Clinical Modification (ICD-9-CM) codes for procedures: 1474, 1475, 1479, 149. These codes have been commonly used in the literature but they are likely to capture other treatments such as injectable antibiotic or corticosteroids.(1) Cases were excluded even if the diagnosis was likely to be associated with anti-VEGF treatment but the code of procedure was outside the selected group specified above. For example, for the 5 diagnoses shown if Figure 2 there were 13,750 cases excluded from further analysis due to this filter. Effects to our estimation caused by the poor specificity of the code were reduced using two methods: first, years 2002-2006 were included as baseline as before 2006 intravitreal anti-VEGF treatments for ophthalmologic use were not licensed; second, we crossed information of age with principal diagnosis. Baseline years provide the picture of the number of cases associated with the codes but not related with anti-VEGF treatments. We considered that AMD only affects people in the age-range 50-59 or above (26) and anti-VEGF are used for specific diagnosis, such as AMD or diabetic macular oedema. Supplementary Table 1 and Supplementary Table 2 show how this information was used in our methods. For the period studied the only approved anti-VEGF drugs for use in public hospitals were Ranibizumab (Lucentis, Novartis) and Bevacizumab (Avastin).

We used the indicators bellow:

- The absolute values of the number of hospital episodes per year. Episodes were then disaggregated by: i) sex, ii) age of the patients (under/over 60 years old), iii) principal diagnosis.
- The number of patient treated per year. To calculate the number of patients, we considered one treatment per person per year, regardless of the number of episodes of care (number of treatments) that occurred in each year.

- The yearly rates of hospital episodes per 100,000 population [(number of episodes per year/annual average resident population per year) x 100,000].
- The age-standardized rates of hospital episodes per 100,000 population by counties per year [(number of episodes by county and year/annual average resident population per county and year)x 100,000] using general demographic information published by Statistics Portugal.(27) County of residence was obtained from the administrative database used in the study. We used the direct method of standardization as described by Beaghole and collegues with standard Portuguese population.(28) The age-standardisation was necessary to control the effect of age heterogeneity across populations living in different counties. Mainland Portugal is divided into 248 counties that correspond to local prefectures with specific administrative and political competences defined by the central government.

Study analysis

We first evaluated the diffusion of treatments across areas, using the mean, minimum and maximum values of the rates of hospital episodes per 100,000 population in 2002, 2006 and 2012. The relative variation coefficient was used to measure the dispersion of the diffusion.

Three time points were selected because they corresponded to: 2002 – the first year included in this study, 2006- the year before the approval of intravitreal injections with anti-VEGF by EMA and 2012 because it was the latest available information when this study started.

To investigate the determinants of geographical diffusion of anti-VEGF treatments we used generalized linear modelling. Considering the longitudinal nature of the data and its non-normal distribution we used Generalized Estimating Equations (GEE).(29) The dependent variable was defined as the yearly rate of hospital episodes per county per 100,000 population. We defined as independent variables: i) the years during which the geographical diffusion was analysed (a linear trend); ii) a dichotomous variable to indicate the year where the drug was authorized in the EU by EMA (Anti-VEGF therapy

availability: 0-not available; 1–available; iii) a dichotomous variable to indicate the availability of an ophthalmology department in the hospital of the patients' county of residence (Ophthalmology department availability: 0-no ophthalmology department; 1–ophthalmology department) and iv) population density (population per squared kilometre) in the county. Information about the availability of ophthalmology departments was obtained in October 2014 from the Health Ministry official website (30). The referral pathway for ophthalmology starts in the general practitioner (GP) according with local referral guidelines. The circuit of the treatment does not interfere with our calculations because we compute treatment ratios based in the county of origin of the patient and that is independent of the hospital where treatment was administered. The model was defined as gamma log link distribution regression model as the rate was expected to be positively skewed with an autoregressive first order matrix representing time dependence within repeated subject.(31) A total of 278 counties were considered as "subjects" with repeated measures. Year and dichotomous variable "anti-VEGF availability" were defined as within subject independent variables. Dichotomous variable "Ophthalmology department availability" and "population density rates" were defined as between subject variables. The analysis was performed using IBM SPSS Statistics 21.0.

Results

The final sample included 98,408 hospital episodes. Figure 1 shows that the total number of episodes increased from 1,815 in 2002 to 25,106 in 2012. This corresponds to a mean annual increase of 32%.

===== FIGURE 1 =====

In 2012, the number of treated patients was six times higher than in 2002, corresponding to a mean annual increase of 24%. The ratio number episodes/number patients was 1.16 in 2002, 1.17 in 2006 and 2.1 in 2012. The most relevant demographic information was the percentage of patients treated who were older than 60 years of age. The figures changed from about 60% in 2002 to 80% in 2012.

Figure 2 shows the five principal diagnoses responsible for the episodes detected. The figure is expected to provide a picture of the growth of the number of episodes per year and number of patients treated per diagnoses. The most common diagnosis was exudative age -related macular degeneration, followed by diabetic macular oedema (diabetes with ophthalmic complications), oedema of the retina, retinal neovascularization, and non-specific AMD. The cumulative percentage of episodes associated with these five diagnoses was 73% in 2012, in contrast with only 16% in 2002. These values corresponded to an increase in the yearly rates of hospital episodes per 100,000 individuals from 17.4 in 2002 to 238.77 in 2012.

===== FIGURE 2 =====

Table 1 gives a summary of the mean, minimum and maximum values in 3 specific years of the rates of hospital episodes per 100,000 population. Both maximum and minimum rate values increased over time. The relative variation coefficient varied from 200% in 2002, to 204% in 2006, and 209% in 2012. The relative coefficient of variation indicates that rates per county have a great dispersion and that this dispersion did not reduce over time. The first quintile always contains rates equal to zero, which means that there are counties without events. In 2002 there were 58 counties in the first quintile (without episodes). The number of counties without episodes reduced over time to 33 in 2006 and 3 in 2012. All the mean values per quintile rose in the period analysed.

===== TABLE 1 =====

Results of the regression analysis are summarized in Table 2. In agreement with the initial prediction and consistent with the introduction of the new treatment with anti-VEGF, the model shows a significant effect of the variable “year”, $p<0.0001$. For each additional year the rate of hospital episodes increased by 28%. The rate was significantly higher after the EMA approval, in Table 2 results for “Anti-VEGF therapy availability”, $p<0.0001$. With the approval of this treatment the rates of hospital episodes increased by 27%. The availability of an ophthalmology department in the hospital of the county (in Table 2 results for “Ophthalmology department availability”) significantly

increased the rates of hospital episodes by 243%, p <0.0001 (compared with counties without). The positive association between the variable "Ophthalmology department availability" and our dependent variable indicates that anti-VEGF treatments were more frequent to patients living near hospitals with ophthalmology departments, which are typically located in areas of median/high population density. There was a positive association between the dependent variable and population density. An increase of 100 persons per square kilometre raised the rates of hospital episodes by 11%. This results show that patients living in rural areas were less frequently treated.

===== TABLE 2 =====

Discussion

With this study we wanted to investigate the diffusion of anti-VEGF treatments for eye disease in Portugal looking for possible determinates and/or barriers. We performed this investigation by characterizing the temporal and geographical distribution of anti-VEGF treatments using codes for specific type of procedures from all episodes performed in public hospitals. Our results show that the number of episodes for the codes analysed was low before the introduction of anti-VEGF treatments. The numbers episodes rose significantly since the treatment was introduced in the country in 2007. The most relevant finding was that patients from small areas without ophthalmology departments near their residence received fewer treatments as revealed by the geographical distribution of episodes. The unequal distribution is puzzling, given the equity-oriented nature of the Portuguese NHS

We consider three possible barriers for the equitable anti-VEGF diffusion related to legal, technical and financial factors. Following the EMA approval of this treatment in 2007 and the NHS coverage decision in 2008 the treatment became legally available at all ophthalmology departments in Portugal. One can thus say that the legal problem was sorted. However technical conditions were imposed for the use of this treatment that included extra training for doctors and that the procedure needed to be performed in the operation theatre.(18) These

technical requirements possibly created financial and service capacity pressures on ophthalmology departments.(1, 4) Indeed, higher rates of treatment were observed mostly in areas around big cities and specialized centres. Smaller hospitals may have taken longer to adopt this treatment due to budget limitations or technical conditions. It should also be mentioned that anti-VEGF therapy was first introduce to treat AMD and then expanded to diabetic macular oedema and central retinal vein occlusion treatment. This certainly increased the rate of hospital episodes but the effect is expected to be similar in all counties.

Regarding financial barriers we can speculate about two main budget limitations that reduced the speed of diffusion of anti-VEGF treatments. The first financial challenge is the cost of the treatment of approximately €1,913 per episode, a figure similar to the United States.(25, 32) In Portugal, hospitals receive a global budget from the government that covers the cost of all drugs and medical devices.(18) During the period included in this study the financing methodology used to allocate resources to the Portuguese NHS hospitals has been subject to several changes. This included the introduction of different unit payment and new incentive programs that rely on quality and cost indicators. These changes to hospital budgets and pressure for cost-containment may have reduced the availability of anti-VEGF treatments in small hospitals concentrating patients in big centres with limited capacity. A second financial barrier for hospitals is the fact that the intravitreal injections need to be administered in an operating room by an ophthalmologist. Typically, patients receive three injections in the first 3 months, followed by monthly visits for assessment and further injections as necessary.(22) These surgical procedures and monthly appointments impose high demands on hospitals (staff and facilities). In a period of tight budgets, expansions in the medical staff or facilities are difficult to implement, these problems have been recently reported by Marko Hawlina, a retinal specialist form Slovenia, quoting results of a survey of the European Union of Medical Specialists.(33) Thus, some hospitals may have delayed the start of these treatments or they may still not be available.

The reasons outlined above have implications for the geographical diffusion of the treatment leading to inequalities. Patients referred from distant cities or rural

areas may have delayed access to treatments. The lower rate of treatments in patients living in areas of low population density may also indicate that these patients are more likely to miss follow-up appointments. Travelling distances may be a barrier to attending appointments as reported by other studies.(34-36) This evidence is a cause of concern because vision loss due to the spectrum of diseases for which anti-VEGF treatments are indicated cannot be restored. This may lead to an increased number of people becoming visually impaired due to treatable causes.

During this study we found some limitations: the lack of specific codes for anti-VEGF injections, the inability to follow patients across different years, the exclusion of the activity in the private sector and the absence of individual data. Limitations caused by non-specific codes have been described in methods. The inability to follow patients across years might have had impact in the ratio episodes/patient that we found. Nevertheless, the county of residence remained unchanged across years ensuring temporal and geographical accuracy of treatment diffusion. Other studies, analysing equivalent temporal periods, also report treatment ratios under 3 per year. These authors explained the low ratios by a higher concentration of patients treated as required (1). Numbers from private treatments were likely to be small because this treatment is expensive and patients tend to look for care in the national health system where treatment is almost free. The lack of individual data limited our analysis of socio-economic determinants such as patient income or education level or other clinical conditions that could restrict the prescription of anti-VEGF therapy. However, with the available data we were able to construct a complex and multivariable model to explain the geographical diffusion and time variation based on a nationally representative database, with many types of hospital settings and geographic areas that would be difficult to perform with a limited sample number of cases.

In brief, the use of anti-VEGF drugs in ophthalmology marked the beginning of effective treatments for age related eye diseases that can lead to severe visual impairment. This study shows that the number of intravitreal procedures increased substantially since anti-VEGF treatments were approved in Portugal but that the diffusion was inequitably distributed. Local restrictions to the

temporal and geographical diffusion seem mostly imposed by financial aspects. These financial constraints may arise, not only, from cuts in budgets in the health care system but also from difficulties for families to fund travel costs. With the aging of the population and the expected growth in conditions such as diabetic retinopathy and age-related macular degeneration, the demand for these treatments is likely to increase.(7) The combination of these factors will maintain pressure on ophthalmology departments delivering eye care. Health authorities need to consider the equitable distribution when planning human and material resources for ophthalmology departments.

Table 1: Age-standardized rates of hospital episodes per 100.000 populations per county in the year 2002, 2006 and 2012. Values show quintiles mean, minimum and maximum values.

Quintile	2002			2006			2012		
	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
1st	0	0	0	0.0001	0	0.0002	0.0013	0	0.0024
2nd	0.0002	0.0001	0.0003	0.0003	0.0002	0.0005	0.0037	0.0024	0.0051
3rd	0.0005	0.0004	0.0008	0.0009	0.0006	0.0013	0.0069	0.0051	0.0091
4th	0.0012	0.0008	0.0017	0.0019	0.0013	0.0026	0.0148	0.0093	0.0221
5th	0.0048	0.0017	0.0231	0.008	0.0026	0.0459	0.0764	0.0222	0.3745
Total	0.0013	0	0.0231	0.0022	0	0.0459	0.0208	0	0.3745

Ratio **Wald chi-square test of significance (95% Confidence Interval)

Table 2: Results of the Generalized Estimating Equation for the rate of hospital episodes per 100.000 population per year and independent variables were: year, Anti-VEGF therapy availability (separating years before and after the drug was authorized by EMEA); Ophthalmology department availability (representing the availability of ophthalmology departments in the hospitals of county of residence) and population density (population per square kilometre in the county). Total number of counties is 278.

Parameter	**IRR***	**p- value**	**95%CI****	
			Lower	**Upper**
Year (from 2002 to 2012)	1.281	<0.001	1.263	1.299
Anti-VEGF therapy availability (0- not available; 1 – available)	1.270	<0.001	1.183	1.362
Ophthalmology department availability (0 - no ophthalmology dept; 1 –ophthalmology dept)	3.430	<0.001	2.566	4.583
Density rate (per 100 persons)	1.113	<0.001	1.095	1.132

*Incidence Rate Ratio **Wald chi-square test of significance (95% Confidence Interval)

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c) Data sharing

No additional data are available.

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Figure legends

Figure 1

Annual number of hospital episodes of anti-VEGF treatments and annual number of treated patients from 2002 to 2012.

Figure 2

Number of hospital episodes associated with the top 5 diagnoses by year.

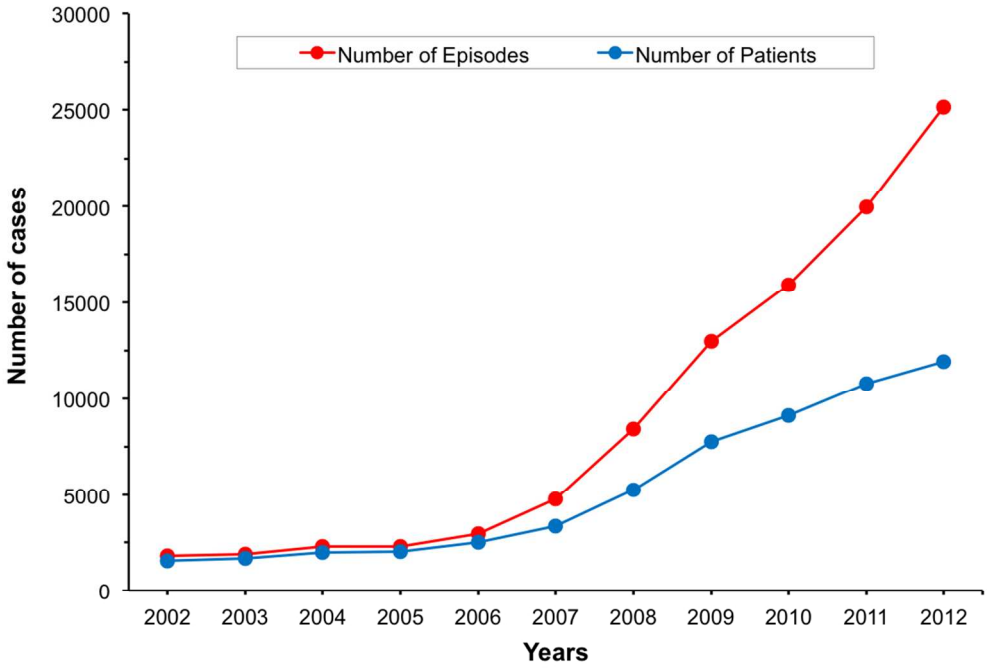

Figure 1: Annual number of hospital episodes of anti-VEGF treatments and annual number of treated patients from 2002 to 2012.

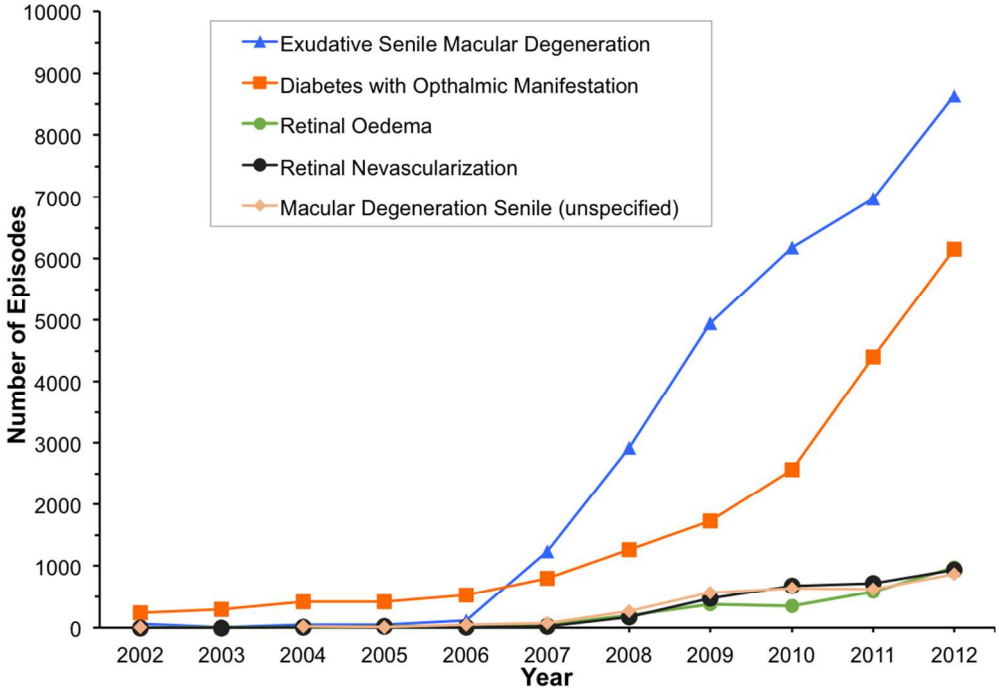

Figure 2: Number of hospital episodes associated with the top 5 diagnoses by year.

Supplementary Table 1 shows episodes distribution per age category and year. There is an increase in the absolute number of episodes for patients older than 50 years (second row from bottom) and percentage of patients with this age range also increases Overall patients older than 50 years represent 90.0% of cases. Age range 40-49 (third row from bottom) represents 5% of total cases. This age-range also shows a decline in the proportion of cases per year through the years, although the absolute mean number of episodes increases from 210.5 in years 2002-2007 to 744.4 in years 2008-2012. The additional number of cases observed in more recent years was associated with diagnosis compatible with anti-VEGF treatment as shown in Supplementary Table 2. In the age-range 20-39 there was a reduction in the proportion of cases across the years. It changes from 10.9% in 2002 to 2.7% in 2012 and the overall percentage for all years is 4.1%. As above, the absolute number of cases increases but is explained by diagnosis compatible with anti-VEGF treatment as shown in Supplementary Table 2. In the age range 0-19 the absolute values for the number of case oscillated and was typically between 50 and 100 cases per year in the years covered, the proportion reduced from 3.6% in 2006 to 0.4% in 2012.

Supplementary Table 1 – Episodes per year and age-range from years 2002 to 2012

Year/Age range	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		2012		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0-19	66	3.6%	44	2.3%	62	2.7%	38	1.6%	67	2.3%	45	0.9%	76	0.9%	94	0.7%	105	0.7%	102	0.5%	90	0.4%	789	0.8%
20-39	197	10.9%	208	11.0%	223	9.8%	200	8.7%	243	8.2%	275	5.8%	374	4.4%	468	3.6%	520	3.3%	654	3.3%	666	2.7%	4028	4.1%
40-49	171	9.4%	165	8.7%	192	8.4%	191	8.3%	242	8.2%	302	6.4%	437	5.2%	620	4.8%	758	4.8%	822	4.1%	1085	4.3%	4985	5.1%
> 50	1381	76.1%	1482	78.0%	1808	79.1%	1876	81.4%	2416	81.4%	4128	86.9%	7535	89.5%	11793	90.9%	14535	91.3%	18387	92.1%	23265	92.7%	88606	90.0%
Total	1815	100%	1899	100%	2285	100%	2305	100%	2968	100%	4750	100%	8422	100%	12975	100%	15918	100%	19965	100%	25106	100%	98408	100%

Supplementary Table 2 shows episodes distribution by diagnosis and age-range for two selected: years 2007 and 2012. These years were chosen because 2007 represents the year before the treatment was approved and 2012 because was the most recent year with complete information available. Diagnoses presented in this table represent 75% of episodes in 2012. This table is presented to provide evidence that the increase in the number of cases included in our data analysis were likely to be associated with anti-VEGF treatments despite the non-specificity of the codes of procedure that were used. The two age ranges in which there was an increase in the number of episodes but the age would raise doubts if they were recommended for anti-VEGF was the age range 20-39 and 40-49 years. When comparing 2007 with 2012 there was an increase of 391 episodes in the age range 20-39 years and 783 cases in the age range 40-49. The seven diagnoses in Supplementary Table 2 correspond to 81% of extra cases found in in the age range 20-39 and to 76% of the extra cases found in the age range 40-49. The seven diagnoses below all have indication for treatment with anti-VGEF. The reminder cases were scattered by several diagnosis. We considered that the amount of cases with scattered diagnosis was relatively low and the analysis was conducted with all episodes and cases detected for these years. The noise that these cases might have caused would be randomly distributed in all counties analysed.

Supplementary Table 2 – Episodes by Principal Diagnosis and Age Category. 2007 and 2012

Principal Diagnoses		2007					2012					2012 vs 2007				
ICD 9 CM	Designation	0-19	20-39	40-49	> 50	Total	0-19	20-39	40-49	> 50	Total	0-19	20-39	40-49	> 50	Total
36252	Exudative Senile Macular Degeneration	0	19	20	1200	1239	0	23	54	8549	8626	0	4	34	7349	7387
25050	Diabetes with Opthalmic Manifestation	0	13	46	740	799	2	117	335	5696	6150	2	104	289	4956	5351
36283	Retinal Oedema	0	4	4	39	47	2	32	53	895	982	2	28	49	856	935
36216	Retinal Nevascularization	6	5	2	14	27	0	94	121	726	941	-6	89	119	712	914
36250	Macular Degeneration Senile (unspecified)	0	0	4	77	81	0	12	10	847	869	0	12	6	770	788
36235	Retina Central Vein Occlusion	0	0	0	17	17	0	6	23	508	537	0	6	23	491	520
36236	Retina Veinous Tributary Occlusion	0	0	0	4	4	0	4	16	605	625	0	4	16	601	621
Others		39	234	226	2037	2536	86	378	473	5439	6376	47	144	247	3402	3840
Total		45	275	302	4128	4750	90	666	1085	23265	25106	45	391	783	19137	20356

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.