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Kui Huang[1]*, Marla B. Sultan[2], Duo Zhou[3], Charles S. Tressler[4] and Jingping Mo[1]

[1]*Epidemiology, Pfizer Inc, 235 East 42nd St, 219/9/41, New York, NY 10017, USA*
[2]*Clinical Affairs, Pfizer Inc, 235 East 42nd St, NY 10017, USA*
[3]*Statistics, Pfizer Inc, 235 East 42nd St, NY 10017, USA*
[4]*Safety Surveillance & Risk Management, Pfizer Inc, 235 East 42nd St, NY 10017, USA*

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***Corresponding author:** Kui Huang, PhD, MPH, Epidemiology, Pfizer Inc, 235 East 42nd St, 219/9/41, New York, NY 10017, USA, Tel: 212-733-1309; Fax: 212-857-3672; Email: Kui.a.Huang@Pfizer.com

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Research Article

Ocular Safety of Intravitreal Injections of Age-Related Macular Degeneration Treatments in a Prospective Observational Cohort Study in Europe

Abstract

Purpose: Estimate the incidence of pertinent ocular adverse events (POAEs) related to intravitreal (IVT)injections for age-related macular degeneration (AMD) treatments in Europe.

Methods: Ophthalmologists prospectively followed patients, who received IVT injection treatment for AMD including Macugen®, Lucentis®, and Avastin® at ophthalmic clinical centers in Europe, and determined outcomes of interest as clinically appropriate up to two years. Main outcomesincluded endophthalmitis, retinal detachment, vitreous hemorrhage, retinal tear, traumatic cataract, and increased intraocular pressure (IOP).

Results: 501 patients from 69 sites in 13 countries were enrolled.The mean age was 73.6 years. Most patients received monotherapy (80.4%), were white (97.4%), and never smoked (65.3%).The total number of IVT injections for AMD treatment was 3,754 among those patients. The incidence of POAEs was low overall (0 to 1.28% per injection, 0 to 6.6% per patient).Increased IOP was the most frequently reported POAE. There was a positive association between the incidence of increased IOP and the number of injections received.Endophthalmitis was not reported.

Conclusions: The incidence of POAEs related to IVT injections in this study was low and similar to that reported in the literature.

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in persons 65 years of age or older in western populations. AMD is a progressive, degenerative disorder of the retinal pigment epithelium (RPE) and neurosensory retina. It is classified broadly into two types: the non-neovascular (non-exudative) and the neovascular (exudative) AMD. Although the non-neovascular form is the most prevalent, accounting for approximately 90% of cases of the disease, it is the neovascular type of AMD that is responsible for the majority of cases of severe vision loss. It is estimated that 3.3% of the European population 65 years or older has neovascular or non-neovascular AMD and that the prevalence is 40% higher in women than men [1].

Until the end of 2004, there was no approved therapy for the treatment of the majority of patients with neovascular AMD, and patients' options consisted of observation and/or laser treatment (thermal and photodynamic). Macugen® (pegaptanib sodium) was the first approved vascular endothelial growth factor (VEGF) antagonist in Europe in 2006, followed by Lucentis® (ranibizumab) in January 2007, and Eylea® (aflibercept) in 2012. Avastin® (bevacizumab) has been used off-label for treatment of this disease since middle of 2006. This study was conducted to estimate the incidence of ocular adverse events related to IVT injections of AMD treatments at ophthalmic clinical centers in Europe.

Materials and Methods

Study design

This was a 2-year, prospective, multinational, observational, cohort study in Europe. The primary objective of the study was to estimate the incidence of ocular adverse events, including endophthalmitis, retinal detachment, vitreous hemorrhage, retinal tear, traumatic cataract, and increased intraocular pressure (IOP) among neovascular AMD patients receiving IVT injections of AMD treatments in the real world setting in Europe over a two-year period. Henceforth, these endpoints were collectively referred to as pertinent ocular AEs (POAEs). The study was initiated in August 2006 and ended in February 2012. The study population consisted of patients who received IVT injection treatment for AMD, the initial treatment was with Macugen, as per the approved summary of product characteristics. Following the initial treatment, patients also received additional AMD treatment with Lucentis or Avastin (off-label use). Treating ophthalmologists prospectively followed study participants and determined outcomes of interest as clinically appropriate. For POAEs, new events as well as worsening of existing events were required to be reported. All POAEs events, relevant medical and ocular history, and serious adverse events (SAEs) in this study were verified against medical charts by monitors. There were no study-

mandated visits. After a patient enrolled in the study, the treating ophthalmologist followed the patient as per usual care.

Statistical method

Descriptive statistics were used to summarize demographics and clinical characteristics among all patients in the study. The primary study endpoints, incidence of POAEs, were examined per patient and per injection. The incidence per injection was calculated as the total number of POAE occurrences divided by the total number of IVT injections received during the study while incidence per patient was the number of patients with POAEs divided by the total number of patients receiving IVT injections during the study. Depending on the nature of events of interest, POAEs were categorized into nonchronic and chronic. Nonchronic events included endophthalmitis, vitreous hemorrhage, traumatic cataract, increased IOP (defined as a significant increase after IVT injection), and hypersensitivity reaction. Retinal detachment and retinal tear were considered chronic POAEs.

The numerator of incidence per injection and patient was calculated differently for non-chronic versus chronic POAEs. For nonchronic events per injection and patient, an occurrence was only counted if the patient received an injection in the eye experiencing the event at the visit prior to event occurrence. For chronic events per injection, the numerator was calculated as follows: only the first occurrence of a POAE was counted, provided that the patient received treatment in the eye experiencing the event at any time in the study before event occurrence. Patients with events occurring in both eyes had both events counted, provided that an injection was administered in the corresponding eye prior to experiencing the event. Incidence per patient for chronic events was calculated in a similar manner; however, a patient was only counted once, i.e. the first time either treated eye experiences a chronic POAE.

Results

In this study, a total of 507 patients were screened from 69 sites in 13 European countries including Belgium, Cyprus, Czech Republic, Denmark, France, Germany, Greece, Ireland, Italy, Poland, Slovakia, Spain, and Sweden. Of these, 501 patients were eligible and enrolled in the study. Slovakia enrolled the most patients (30.9%) followed by the Czech Republic (14.8%) and Greece (11.4%). Most patients (80.4%) received Macugen monotherapy. A total of 425 patients (84.8%) completed the study.

Out of 76 patients that discontinued from the study, the most frequent reason for discontinuation was that the patients were unwilling to continue their participation in the study (n=31). Seven patients died for reasons unrelated to the study treatment based on investigators' assessment and 1 patient discontinued the study due to an unrelated AE.

Table 1 summarizes demographic and other baseline characteristics. Few patients were ≤50 years of age at the time of enrollment into the study (1.0% of patients overall).The mean age was 73.6 years. Most patients (97.4%) were white, and the racial origins of the remaining patients (2.6%) were unspecified. Most patients were either self-reported: never smokers (65.3%) or ex-smokers (25.9%). Only 8.4% of patients were current smokers. 11.8% of patients received AMD treatment in both eyes.

For relevant medical history, angina pectoris was the most frequently reported comorbidity overall, and occurred in 18.6% of patients. Type 2 diabetes mellitus was reported in 16.0% of patients, and myocardial infarction was reported in 10.0% of patients. For ocular history related to POAEs based on medical records, 59.5% presented with cataract and 8.8% presented with glaucoma.

Overall, the total number of IVT injections for AMD treatment was 3,754 among these patients. The incidence of POAEs was low overall and ranged from 0 to 1.28% per injection and0 to 6.6% per patient (Tables 2,3). Increased IOP was the most frequently reported POAE (1.28% per injection and 6.6% per patient), with a total of 48 occurrences in 33 patients. Vitreous hemorrhage, traumatic cataract, hypersensitivity reaction, retinal tear, and retinal detachment were reported at an incidence rate of 0.03% to 0.11% per injection and 0.2% to 0.8% per patients. Endophthalmitis was not reported during the study.

Additional exploratory analyses were conducted on incidence of increased IOP per patient using a generalized estimation equation analysis method.There was a positive association between the incidence of increased IOP and the number of injections received.

Table 1: Demographic and Baseline Characteristics.

	Number (%) of Patients
	Total
Patient N	**501**
Eye N	**560**
Age (years)*	
≤50	5 (1.0)
51 – 64	79 (15.8)
65 – 74	149 (29.7)
≥75	268 (53.5)
Mean (SD)	73.6 (8.7)
Range	48-93
Gender *	
Male	194 (38.7)
Female	307 (61.3)
Smoking status	
Current smoker	43 (8.6)
Ex-smoker	130 (25.9)
Never smoked	327 (65.3)
Missing	1 (0.2)
Treated eye,†.‡	
Right eye	222 (44.3)
Left eye	220 (43.9)
Both eyes	59 (11.8)

Abbreviations: AMD = age-related macular degeneration, N = number of patients in each treatment group, SD = standard deviation

*Percentages were calculated using Patient N as the denominator.

†At Baseline

‡Treated Eye was determined from injection data (Macugen, Avastin, and Lucentis) and identifying which eye(s) for a patient received injections. Patients may have had right, left, or both eyes defined as treated eye.

Treated eye N was higher than Patient N as instances of 'both eyes' treated were counted twice.

Table 2: Incidence of Treatment-Emergent Pertinent Ocular Adverse Events per Injection*.

	Incident Rate (%*) per Injections
	Total (N=501; n=3754)
Increased IOP	48 (1.28)
Vitreous hemorrhage	4 (0.11)
Traumatic cataract	4 (0.11)
Hypersensitivity reaction	2 (0.05)
Retinal detachment	1 (0.03)
Retinal tear	1 (0.03)
Endophthalmitis	0 (0)

Abbreviations: AMD = age-related macular degeneration, N = number of patients in each treatment group, n = number of injections, POAE = pertinent ocular adverse event, IOP = intraocular pressure

*Incidence rate per injection: the number of specific POAEs divided by the total number of injections (n) received in treated eye(s)

Table 3: Incidence of Treatment-Emergent Pertinent Ocular Adverse Events per Patient*.

	Total (N=501)
Increased IOP	
Incidence, n (%)	33 (6.59)
95% CI: Lower	0.0458
95% CI: Upper	0.0913
Vitreous hemorrhage	
Incidence, n (%)	4 (0.80)
95% CI: Lower	0.0022
95% CI: Upper	0.0203
Traumatic cataract	
Incidence, n (%)	3 (0.60)
95% CI: Lower	0.0012
95% CI: Upper	0.0174
Hypersensitivity reaction	
Incidence, n (%)	2 (0.40)
95% CI: Lower	0.0005
95% CI: Upper	0.0143
Retinal detachment	
Incidence, n (%)	1 (0.20)
95% CI: Lower	0.0001
95% CI: Upper	0.0111
Retinal tear	
Incidence, n (%)	1 (0.20)
95% CI: Lower	0.0001
95% CI: Upper	0.0111
Endophthalmitis	
Incidence, n (%)	0 (0)
95% CI: Lower	0
95% CI: Upper	0.0073

Abbreviations: AMD = age-related macular degeneration, N = number of patients in each treatment group, n = number of patients with a response, POAE = pertinent ocular adverse event, IOP = intraocular pressure, CI = confidence interval, SD = standard deviation

*Incidence rate per patient: the number of patients with specific POAEs divided by the total number of patients that received injections in treated eye(s)

The odds of increased IOP was increased by a factor of 1.128 for each additional injection (p=0.0003) (95%CI: 1.057, 1.204).No statistical difference was found in the incidence of increased IOP between patients with a history of increased IOP or glaucoma versus patients without. There was no significant difference between the treating ophthalmologists' experience with IVT injections, expressed as either ≥20 IVT injections per month in the past year or <20 IVT injections per month in the past year.

Discussion

Since 2006, VEGF inhibitors, including Macugen, Lucentis, and Avastin (off-label use in this indication) have become the leading class of drug used to treat neovascular AMD in the EU and the United States. All 3 pharmaceuticals are administered via IVT injection.

The incidence of IVT injections related ocular AEs has declined over the recent years. In 2004 a meta-analysis using data from 14,866 IVT injections in a mixed disease population was the initial largest source of information on the incidence of POAEs associated with IVT injections [2]. The incidence of endophthalmitis was 0.3% per injection, retinal detachment was 0.9% per injection, and intraocular hemorrhage was 1.3% per injection. Since then, the incidence of IVT injection-related endophthalmitis in a mixed disease population ranges from 0 to 0.2% and the number of IVT injections ranged from 3,938 to 105,536 injections [3-7]. The incidence of IVT injection-related endophthalmitis in AMD populations has been reported to be low, ranging from 0% to 0.16% per injection and the number of IVT injections in these studies ranged from 2,000 to 40,903 [8-12].

The incidence of IVT injection-related retinal detachment among AMD populations ranges from 0% to 0.16%per injection with the number of IVT injections of these studies ranges from 4,303 to 27,736 [9-11]. The incidence of IVT injection-related retinal tear and vitreous hemorrhage among AMD populations was 0.06% and 0.23% per injection, respectively and the number of IVT injections was 27,736 [10]. The incidence of IVT injection-related traumatic cataract in AMD populations was 0% (the range of IVT injections in these studies was 345 to 1,114) [12,13]. Further review of the literature reveals that the incidence of the IVT injection-related retinal detachment in a mixed disease population was 0 to 0.019% per injection and the range of IVT injections in these studies was from 1,584 to 35, 942 [7,14], vitreous hemorrhage was 0% per injection (the number of IVT injections in this study was 3,938) [23]. The incidence of IVT injection-related hypersensitivity reactions is unknown. However, Frenkel et al. [12] reported that one eye of a patient developed lid swelling in a mixed disease population (0.29% per injection).

Findings in this study are consistent with the low incidence rate of POAEs associated with IVT injections reported in the literature since 2007. No instances of endophthalmitis were reported in this study. In addition, the instances of vitreous hemorrhage, hypersensitivity reaction, traumatic cataract, retinal tear, and retinal detachment were infrequent per injection (0 to 0.1% of injections) and per patient (0 to 0.8% of patients).In this study, increased IOP was the most frequently reported POAE (6.6% per patient), which is consistent with the reported incidence of increased IOP in a mixed disease population (ranges from 3.4% to 11% per patient) [15,16].

Further, the study reported 2.1% of patients with increased IOP at baseline. After baseline, the incidence of increased IOP at month 0-6, 6-12, 12-18, and 18-24 were 2.8%, 1.7%, 1.8%, and 3.9% respectively. Additionally, there was a positive association between the incidence of increased IOP and the number of IVT injections received.

This association between repeated IVT injections and elevation in IOP was previously noticed in a retrospective chart review [17]. The association may be confounded by age. As people age, IOP is expected to increase [18]. Aside from aging, other possible contributing mechanisms for an elevation of IOP include molecular size of the therapeutic agent, changes in the trabecular meshwork, changes in corneal hysteresis, changes in scleral rigidity with increasing age, and repeated IVT injections [17,19-22].

This prospective study enrolled 501 AMD patients from ophthalmic clinics in 13 European countries and followed them through the normal medical practice. The observed low incidence of IVT injection related POAEs in this study may be attributed to several factors, including an educational program undertaken to support Macugen use, physician experience with IVT injections, better aseptic technique to prevent injection-related infections [23], and availability of IVT injection treatment guidelines [24]. Additionally, it seems that the practicing ophthalmologist may have become more proactive in screening and treating predisposing conditions before IVT injection [25].

Although all reported POAE events and SAEs were validated against the patient's medical chart to ensure accuracy in the study, one major limitation of the study is that significant IOP increases after IVT injection were collected based upon treating ophthalmologists' discretion. This results in a limitation of the understanding of the full magnitude of increased IOP for an injection and the full occurrence of increased IOP over the entire treatment period.

In summary, this prospective, observational study evaluated ocular safety among patients receiving IVT injection of AMD treatments in real world settings in Europe. The incidence of POAEs in this study was low and similar to that reported in the literature. With continued use of IVT injections, increased IOP should be monitored thoroughly, with a comparison of baseline IOP and post-injection IOP over the course of treatment.

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Contributors

Involved in Conception and design of study (K.H., J.M.); Analysis and interpretation of data (K.H., D.Z., M.B.S., C.S.T.); Data collection (K.H.); Statistical expertise (D.Z.); Literature search (K.H., M.B.S., C.S.T.); Writing the manuscript (K.H., D.Z., M.B.S., C.S.T., J.M.); Critical revision of the manuscript (K.H., D.Z., M.B.S., C.S.T., J.M.) and Final approval of the manuscript (K.H., D.Z., M.B.S., C.S.T., J.M.).

Disclosure

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Conflict of Interest

All authors are employees of Pfizer Inc.

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Informed consent

The study was performed with informed consent and following all the guidelines for non-interventional studies required by local laws and regulations.

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