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Pharmacovigilance in ophthalmology in Switzerland: an analysis of the most frequently reported ocular adverse drug reactions within the last 25 years

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Summary

AIMS OF THE STUDY: Although systemic drugs can exert local effects on the eye, ophthalmology is a medical specialty with perhaps the fewest assessed adverse drug reactions (ADRs), representing a particular challenge in pharmacovigilance. Our aim was to quantify ADRs in ophthalmology in Switzerland, with a focus on angiogenesis inhibitors.

METHODS: Individual case safety reports (ICSRs) on suspected ADRs reported in Switzerland from January 1991 to June 2016 were extracted from the WHO Global ICSR database, VigiBase™. ICSRs were analysed in relation to treatment duration, patient age, route of administration, patient sex and reported symptoms.

RESULTS: A total of 80,515 ICSRs were reported in Switzerland during the reference period. Reactions linked to eye disorders accounted for 2793 (3.5%) cases. The main Anatomic Therapeutic Chemical / Defined Daily Dose drug classes associated with eye disorders were drugs acting on the nervous system (27.7%) followed by drugs “acting on sensory organs” (20.2%) and antineoplastic agents (18.0%). Most cases involved adult patients (70.6%). Patients over 60 years accounted for 815 (29.2%) ICSRs, and reactions in children were significantly less frequent (8.2%). Older patients were exposed to a higher number of drugs, and the majority of serious reactions involved children and older patients. A significant positive correlation between polypharmacy and seriousness of reported reactions was observed. The reported drugs were categorised as “suspected” in 51.1%, “concomitant” in 43.3% and “interacting” in 2.6% of cases. “Visual impairment” was the most commonly reported adverse reaction, experienced by 635 (22.7%) of patients (7.2% of all reported eye-related symptoms). The majority of reactions were transient, as 4173 (47.1%) completely resolved. Severe reactions included fatal outcome in 18 patients (0.6%) and blindness in 78 patients (2.6%). Since

2000, the intravitreal vascular endothelial growth factor (VEGF) inhibitors bevacizumab, aflibercept and ranibizumab accounted for 99 ICSRs. Retinal haemorrhage (reporting odds ratio [ROR] 10.36, 95% confidence interval [95% CI] 2.65–40.50; $p < 0.001$), blindness (ROR 3.73, 95% CI 1.08–12.96; $p = 0.04$) and uveitis (ROR 6.91, 95% CI 1.64–29.13; $p = 0.01$) were significantly more frequently reported for aflibercept than for bevacizumab and ranibizumab.

CONCLUSIONS: ADRs that affect the eye represented 3.5% of all pharmacovigilance reports during the reporting period. Whereas retinal haemorrhage and uveitis are known adverse reactions to angiogenesis inhibitors, the reported cases of blindness and death should heighten awareness of potential safety issues associated with VEGF inhibitors for the treatment of proliferative eye disorders.

Keywords: adverse drug reaction, adverse drug event, macular degeneration, retinopathy, monoclonal antibody, drug safety, patient safety, signal detection, disproportionality analysis, pharmacoepidemiology

Introduction

Ophthalmology is one of the medical specialties for which the fewest assessed adverse drug reactions (ADRs) have been reported, which represents a particular challenge in pharmacovigilance [1]. Numerous systemic drugs produce adverse effects that can involve the eye. For example, anticholinergic drugs such as antihistamines, tricyclic antidepressants, sleep aids or cold preparations can lead, among other adverse reactions, to blurred vision and impaired stability in the upright position; patients under the influence of these side effects thus have a tendency to fall [2]. However, topically applied ocular drugs may be systemically absorbed to a significant extent, resulting in widespread adverse side effects in both the eye and other regions of the body [3]. In particular, new ocular drugs, such as vas-

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cular endothelial growth factor (VEGF) inhibitors, which have increasingly been prescribed since their approval in the middle of the last decade, are potentially related to numerous systemic ADRs.

Several reports have indicated an association between ocular ADRs and systemic drugs, but there have been only a few systematic reviews to date [1]. With an increased focus on the safety of these medications, however, more studies are needed to reach further significant conclusions on signals emerging from retrospective studies. Ocular ADRs are frequent and the majority of these events are innocuous for the patients, although detrimental reactions, including fatal ADRs and blindness, have been reported and need to be effectively prevented to safeguard patients and reduce strain on the health system. Visual impairment and blindness are a considerable economic burden, which increases with the degree of visual impairment, for affected persons, their caregivers and society at large [4].

The use of anti-angiogenic therapy imposes potential risks for ocular ADRs. VEGF inhibitors have revolutionised the treatment of retinal disease with an impact on retinal pathologies probably even greater than in oncology, but despite the apparent safety of the small doses used for treating eye disease, these agents are highly potent [5]. Over the past 15 years, a disproportionate increase in cardiovascular and cerebrovascular events has been observed in patients treated with ranibizumab [5]. However, systematic reviews have reported contradictory results, showing low rates of reported serious adverse events after anti-VEGF injections [6]. The incidence of blindness as an adverse event is relevant; increased reporting of endophthalmitis after the topical administration of bevacizumab was observed [5], indicating a risk for this debilitating adverse effect. Although the prognosis for endophthalmitis has improved significantly with advances in antibiotic treatment and vitreoretinal surgery, the number of patients requiring enucleation or evisceration remains significant [7]. Therapeutic approaches using anti-VEGF medications thus require increased attention to safety.

Drugs in this class show diverse pharmacokinetics and pharmacodynamics; for example, bevacizumab is more likely than ranibizumab to induce immune activation and to remain in the systemic circulation. Thus, bevacizumab administration creates a higher risk of systemic adverse events [8].

Current legislation in Switzerland compels any individual who professionally dispenses or administers therapeutic products to humans or animals to notify the Swiss Agency for Therapeutic Products (Swissmedic) of any serious and previously unknown ADRs or quality defects. Spontaneous reporting systems have an important role in the investigation of rare and unpredictable ADRs such as adverse events in ophthalmology. In addition, the collection of these data allows the early detection of ADRs in the post-marketing phase.

The aim of the present study was to quantify ADR reports in ophthalmology in Switzerland by identifying frequencies in spontaneous reports listed in a global database. Our investigation sought to identify the number of cases in ocular pharmacovigilance and to support the requirement for ongoing surveillance and large population-based studies to investigate these outcomes.

Materials and methods

Study design

This was a retrospective cohort study using registry data, with a base cohort consisting of all ADRs associated with the system organ class term “eye disorders” [1]. An important focus of our analyses was new ocular drugs licensed in Switzerland in the past 15 years, the majority of which are anti-VEGF agents approved in Switzerland since the middle of the last decade. We reviewed individual case safety reports (ICSRs) submitted in Switzerland between January 1991 and June 2016. ADRs were analysed with respect to reporting rate per year, age and sex of the patient, and reported symptoms. Patients were grouped based on their age by decade and reported symptoms were described according to MedDRA terminology.

Data source

ICSRs were obtained using the online software VigiLyze™, which allows registered users to access data from VigiBase™, the world’s largest spontaneous ADR system, with more than 8.4 million reports from 104 countries compiled since the WHO international drug monitoring programme started in 1968 [9]. VigiLyze™ allows users to examine data on ADRs using various filters to facilitate data acquisition and to download additional information on the ICSR. VigiBase™ is a registry database with no access to clinical or laboratory data. Therefore, the causal relationship between drug and ADR could not be formally assessed [10].

Data adjustment

Many data were adjusted for the statistical analysis, for example by removing redundancy and bringing the variables into alignment – such as by avoiding repeated terms and synonyms – thus promoting an unambiguous interpretation of the available information while retaining the original content of the report. Duplicate records were also systematically removed. A relevant number of ADR reports included only an approximate duration of the event. Where only the month and year of the start or stop of an ADR were reported, we counted the indicated month as a full month. Where only the year was indicated, we excluded the corresponding ADR from the analysis of event duration, indicating it as “unknown”. A similar approach was adopted by Blaser et al. [11] in an analogous study. A similar readjustment was performed in relationship to the individual reporting the single ADR to the authority: when more than one individual was indicated as reporter, only the most competent was considered for the analysis. For example, when a physician and a layman were listed as reporters of the same ADR, only the former was taken into account. While aligning the fields related to the outcomes of the ADRs, only the term pertaining to the most disabling condition – in accordance with the seriousness criteria of the event – was considered.

Polypharmacy is not unequivocally defined in the scientific literature. In our study, we applied the most commonly used definition for polypharmacy, namely the condition of taking five or more medications daily [12]. Missing data or data insufficiently itemised to allow correct categorisation were classified as “unknown” and represented an independent statistical category.

Statistical analysis

Descriptive statistics were used to summarise and describe the data. The linear correlation between the number of drugs and the rate of serious ADRs was established as the coefficient of determination and was highest when the data were plotted on a simple linear regression model. Reporting odds ratios (RORs), seen as the pharmacovigilance equivalent of the odds ratio (OR), 95% confidence interval (CIs), and p-values were calculated to measure disproportionality for drug-reaction pairs, comparing each of the three anti-VEGF drugs with the other two [13]. Fisher's exact test was used as a nonparametric statistical test of the null hypothesis that no associations existed between two different RORs as categorical variables against the alternative hypothesis that there was an association between the variables. Values of $p < 0.05$ were considered significant.

All statistical analyses were performed using SPSS Statistics (developed by IBM, Armonk (NY), version 25.0 (2017), software package for Mac) and MATLAB (developed by MathWorks, Natick (MA), version R2017b, software package for Mac).

Results

Overview and flow chart

ICSRs associated with eye disorders reported in Switzerland from January 1991 to June 2016 were selected from the WHO Vigibase. Following data adjustment and the removal of duplicates, we obtained 2793 ICSRs corresponding to 6521 drug-reaction pairs (fig. 1). Ocular adverse reactions constituted a small proportion (3.5%) of all ICSRs reported in Switzerland during the period of interest (to-

tal number of reports 80,515). Nevertheless, underreporting could be an important limitation of spontaneous reporting systems for ADRs such as the WHO Vigibase, leading to biased data and possibly false conclusions.

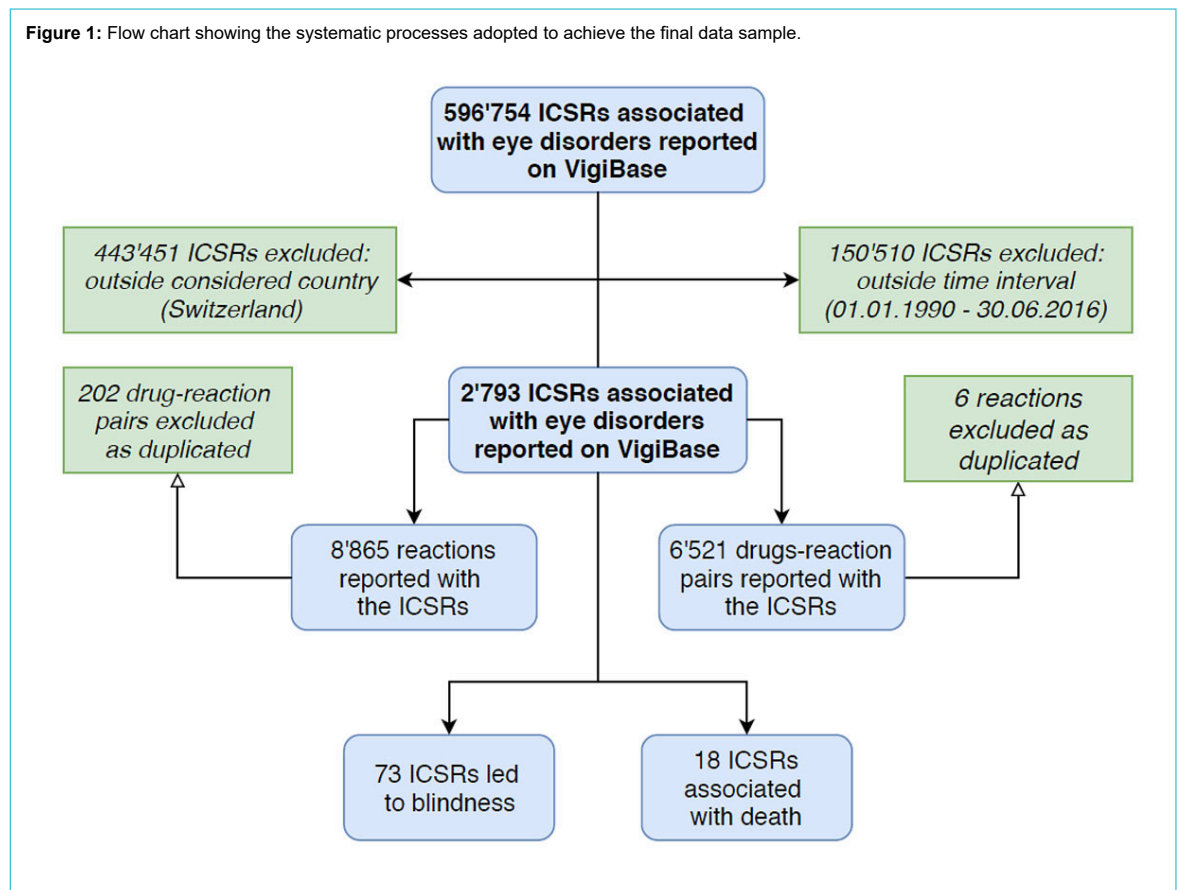
Most frequently implicated drugs and drug-reaction pairs

The main Anatomic Therapeutic Chemical / Defined Daily Dose (ATC/DDD) drug group associated with eye disorders comprised medications acting on the nervous system (ATC/DDD class N), with 774 (27.7%) ICSRs attributed to this drug class. This was followed by 563 (20.2%) ICSRs associated with drugs acting on sensory organs (ATC/DDD class S), 503 (18.0%) representing antineoplastic agents (ATC/DDD class L), and 390 (14.0%) representing dermatological medications (ATC/DDD class D).

Table 1 lists two binary variables, polypharmacy and seriousness of the adverse reaction, and shows their association with the medications described in the ICSRs, the gender and age of patients, and the qualification of the individual who reported the adverse reaction. The ten listed medications were the most frequently reported, regardless of the relationship between medication and ADR (suspected, concomitant or interacting). Taken together, these drugs accounted for 773 (27.7%) drug-reaction pairs, among which the most frequently reported ATC/DDD drug group denoted the trend for all reports, with 40% of drugs acting on the nervous system.

The majority of cases involved adult patients (70.6%); patients aged over 60 years accounted for 815 (29.2%) ICSRs whereas reactions reported in children were significantly less frequent (8.2%). An analysis of patient age revealed

Figure 1: Flow chart showing the systematic processes adopted to achieve the final data sample.



an interesting U-shaped correlation with the seriousness of the adverse drug reaction: children and older patients were more likely to experience serious events than adult patients aged 20–70 years. A similar trend was not observed for the frequency of multidrug therapy: in general, older patients appeared to be exposed to a larger number of medications than younger patients. The only exception to this observation was small children aged under 10 years, who had similar values to patients aged 60–80 years (26.4%).

Health professionals were the main reporters, associated with three out of four ICSRs (75.2%). Overall, physicians had higher reporting rates for ADRs evaluated as serious (57.5%) compared with lay consumers (42.9%).

Given the prevalence of patients receiving several drugs simultaneously, we performed a statistical analysis to investigate the correlation between the number of concurrently ingested drugs and the seriousness of ADRs in the affected patients (fig. 2). The majority of ICSRs pertained to patients who had taken a single drug (1326 ICSRs). In this group of patients, only 576 (43.4%) ICSRs were assessed as serious. This percentage increased linearly: for five concurrently ingested drugs – the definition of polypharmacy – it reached 49.6% of serious ICSRs and for nine concurrently ingested drugs, it reached a maximum, with three out of four ICSRs assessed as serious (75.0%). Our sta-

tistical analysis included up to 10 concurrently ingested drugs, as beyond this number the proportion of ICSRs in each group was insufficient to allow a consistent analysis, showing a reverse trend. This may be due to statistical bias caused by the small number of patients included and the non-representative population sample.

Table 2 displays the analysis of causal relationships between drugs and adverse reactions using data derived from the ICSRs as variables. A suspected relationship between drug and event was identified for half of the drug-reaction pairs (51.1%). Of the remaining pairs, most were assessed as concomitant (43.3%), with only a few classified as in-

Figure 2: Linear correlation between number of concurrent ingested medications and rate of serious ADRs

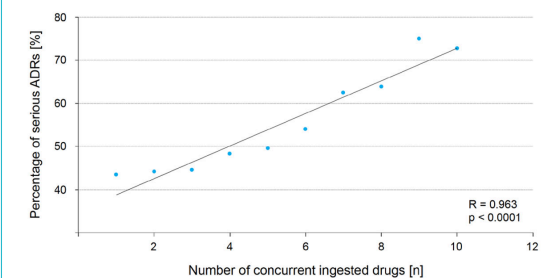


Table 1: Number and percentage of cases associated with polypharmacy and serious events, by name of implicated drug, sex and age of the patient, and qualification of the reporting figure.

		Total cases		Polypharmacy				Serious ADR			
		n	%	Yes		No		Yes		No	
				n	%	n	%	n	%	n	%
Name of the drug	Acetylsalicylic acid	147	5.3%	46	31.3%	101	68.7%	21	14.3%	17	11.6%
	Paracetamol	90	3.2%	35	38.9%	55	61.1%	22	24.4%	10	11.1%
	Lorazepam	78	2.8%	33	42.3%	45	57.7%	15	19.2%	9	11.5%
	Venlafaxine	73	2.6%	52	71.2%	21	28.8%	13	17.8%	21	28.8%
	Pantoprazole	72	2.6%	27	37.5%	45	62.5%	13	18.1%	5	6.9%
	Ranibizumab	57	2.0%	52	91.2%	5	8.8%	38	66.7%	4	7.0%
	Fingolimod	67	2.4%	59	88.1%	8	11.9%	53	79.1%	12	17.9%
	Atorvastatin	66	2.4%	29	43.9%	37	56.1%	5	7.6%	8	12.1%
	Latanoprost	64	2.3%	58	90.6%	6	9.4%	29	45.3%	20	31.3%
Mirtazapine	59	2.1%	33	55.9%	26	44.1%	8	13.6%	8	13.6%	
Sex of the patient	Male	990	35.4%	163	16.5%	827	83.5%	469	47.4%	309	31.2%
	Female	1651	59.1%	279	16.9%	1372	83.1%	756	45.8%	587	35.6%
	Unknown	152	5.4%	5	3.3%	147	96.7%	77	50.7%	62	40.8%
Age of the patient (years)	0–9	91	3.3%	24	26.4%	67	73.6%	56	61.5%	23	25.3%
	10–19	138	4.9%	11	8.0%	127	92.0%	76	55.1%	33	23.9%
	20–29	197	7.1%	17	8.6%	180	91.4%	74	37.6%	68	34.5%
	30–39	260	9.3%	27	10.4%	233	89.6%	109	41.9%	84	32.3%
	40–49	365	13.1%	53	14.5%	312	85.5%	175	47.9%	112	30.7%
	50–59	336	12.0%	54	16.1%	282	83.9%	154	45.8%	121	36.0%
	60–69	366	13.1%	91	24.9%	275	75.1%	157	42.9%	130	35.5%
	70–79	310	11.1%	91	29.4%	219	70.6%	168	54.2%	90	29.0%
	80–89	132	4.7%	42	31.8%	90	68.2%	80	60.6%	32	24.2%
	90–99	6	0.2%	3	50.0%	3	50.0%	4	66.7%	2	33.3%
	100+	1	0.04%	0	0.0%	1	100.0%	0	0.0%	1	100.0%
Reporter qualification	Consumer	245	8.8%	25	10.2%	220	89.8%	105	42.9%	140	57.1%
	Physician	1692	60.6%	326	19.3%	1366	80.7%	973	57.5%	526	31.1%
	Pharmacist	217	7.8%	37	17.1%	180	82.9%	107	49.3%	110	50.7%
	Lawyer	2	0.1%	0	0.0%	2	100.0%	2	100.0%	0	0.0%
	Other health professional	162	5.8%	16	9.9%	146	90.1%	63	38.9%	98	60.5%
	Other	203	7.3%	0	0.0%	190	93.6%	0	0.0%	0	0.0%
	Unknown	272	9.7%	30	11.0%	242	89.0%	105	38.6%	84	30.9%

teracting (2.6%). The duration of ADRs was not normally distributed, shorter ADRs being significantly more prevalent than longer reactions. The range between the shortest and the longest ADR was from 1 day to several years, with a median duration of about 8 days. These data have to be interpreted with caution as only 27.8% of the drug-reaction pairs provided relevant data.

Most frequent reactions and principle outcomes

In addition to evaluating the most frequently implicated medications and their relationship with the ICSRs, we assessed the most common types of ADR. From a total of 8865 different reported reactions and 2793 ICSRs notified, each patient presented with an average of 3.17 symptoms. A total of 635 (22.7%) patients experienced “visual impairment” after medication; this was the symptom most commonly reported and constituted 7.2% of all reported symptoms. This was followed by “eyelid oedema” in 206 patients (7.4%), “vision blurred” in 201 patients (7.2%), “diplopia” in 158 patients (5.7%), “eye irritation” in 128

patients (4.6%), “mydriasis” in 121 patients (4.3%) “eye pain” in 112 patients (4.0%), “ocular hyperaemia” in 91 patients (3.3%), “periorbital oedema” in 78 patients (2.8%), and “dry eye” in 63 patients (2.3%). Less frequent but highly relevant ADRs included fatal reactions, with death reported for 18 (0.6%) patients, and “blindness” for 73 (2.6%) patients.

The majority of reactions were temporary, as 4173 (47.1%) resolved completely. One in every three resolved reactions did not resolve completely: 1321 (14.9%) reactions were permanent and 106 (1.2%) led to long-term sequelae. For 669 (7.5%) reactions, resolution was ongoing, and for more than one in four reactions the outcome could not be determined because of missing data (28.7%).

The best prognosis was observed for mydriasis, as 58 (71.1%) reactions were completely resolved. Other common reactions with particularly positive outcomes were periorbital oedema (62.8%), eyelid oedema (62.1%) and diplopia (53.1%). However, we also identified recurring reactions with outcomes that were frequently negative. For

Table 2: Characterisation of the causal relationship between drug and reaction for the different ICSRs sorted by involved medication, duration of the ADR, drug’s route of administration and drug’s indication.

		Total cases		Characterisation					
		n	%	Suspected		Concomitant		Interacting	
				n	%	n	%	n	%
Name of the drug	Acetylsalicylic acid	147	2.3%	33	22.4%	109	74.1%	5	3.4%
	Paracetamol	92	1.4%	27	29.3%	61	66.3%	4	4.3%
	Lorazepam	79	1.2%	33	41.8%	44	55.7%	2	2.5%
	Venlafaxine	73	1.1%	45	61.6%	27	37.0%	1	1.4%
	Pantoprazole	72	1.1%	28	38.9%	43	59.7%	1	1.4%
	Fingolimod	67	1.0%	51	76.1%	14	20.9%	2	3.0%
	Atorvastatin	66	1.0%	30	45.5%	35	53.0%	1	1.5%
	Latanoprost	65	1.0%	48	73.8%	16	24.6%	1	1.5%
	Mirtazapine	61	0.9%	20	32.8%	40	65.6%	1	1.6%
Esomeprazole	59	0.9%	35	59.3%	24	40.7%	0	0.0%	
Duration of the ADR	1 day	528	7.9%	438	83.0%	77	14.6%	13	2.5%
	2 days	119	1.8%	88	73.9%	25	21.0%	6	5.0%
	3 days	79	1.2%	59	74.7%	16	20.3%	4	5.1%
	4 days	49	0.7%	35	71.4%	11	22.4%	3	6.1%
	5 days	38	0.6%	33	86.8%	5	13.2%	0	0.0%
	6 days	48	0.7%	36	75.0%	10	20.8%	2	4.2%
	7 days	41	0.6%	35	85.4%	6	14.6%	0	0.0%
	8 days	43	0.6%	33	76.7%	10	23.3%	0	0.0%
Route of drug administration	Enteral	3170	48.6%	1669	52.6%	1351	42.6%	150	4.7%
	Parenteral	798	12.2%	635	79.6%	152	19.0%	11	1.4%
	Topical ocular	373	5.7%	336	90.1%	36	9.7%	1	0.3%
	Respiratory	60	0.9%	23	38.3%	37	61.7%	0	0.0%
	Topical (not on the eye)	57	0.9%	46	80.7%	11	19.3%	0	0.0%
	Unknown	481	7.4%	287	59.7%	193	40.1%	1	0.2%
No data	1582	24.3%	442	27.9%	1126	71.2%	14	0.9%	
Drug indication	Depressive episode or disorder	119	1.8%	82	68.9%	18	15.1%	19	16.0%
	Essential hypertension	113	1.7%	53	46.9%	59	52.2%	1	0.9%
	Glaucoma	92	1.4%	86	93.5%	6	6.5%	0	0.0%
	Osteoporosis	52	0.8%	37	71.2%	15	28.8%	0	0.0%
	Epilepsy	57	0.8%	35	61.4%	15	26.3%	7	12.3%
	Diabetes	43	0.6%	19	44.2%	24	55.8%	0	0.0%
	Multiple sclerosis	69	1.0%	67	97.1%	2	2.9%	0	0.0%
	Migraine	39	0.6%	28	71.8%	11	28.2%	0	0.0%
	Asthma	30	0.4%	12	40.0%	17	56.7%	1	3.3%
	Disorder of lipid metabolism	28	0.4%	18	64.3%	10	35.7%	0	0.0%
	Unknown	226	3.4%	98	43.4%	128	56.6%	0	0.0%
	No data	3830	57.0%	1586	41.4%	2165	56.5%	79	2.1%

example, one out of five reactions leading to visual impairment did not recover (21.1%), and for dry eye 18 (28.6%) reactions were permanent.

Most frequent reactions and ADRs comparison among VEGF inhibitors

VEGF inhibitors are approved in Switzerland for the treatment of diseases affecting the eye that have neovascularisation as the main pathophysiological mechanism. At present, three VEGF inhibitors account for the majority of ocular disorders notified in Switzerland since their approval: of a total of 99 (3.5%) ICSRs reported, 57 (57.6%) represented patients treated with ranibizumab, 33 (33.3%) with aflibercept and 10 (10.1%) with bevacizumab. The first ICSRs pertaining to VEGF inhibitors were reported in 2006, but most ADRs were reported between 2012 and 2016 (76 ICSRs corresponding to 76.8% of patients).

An increasing trend was observed in relation to patient age: for every ICSR reported for a child aged under 2 years, 45 were reported for patients older than 65 years. Female patients were more likely to experience adverse events involving anti-neovascularisation agents: 55.6% of ICSRs concerned women and only 17.2% involved male patients.

Table 3 lists the most common reactions reported in association with each of the three cited VEGF inhibitors. A total of 159 reactions were notified, comprising 106 (66.7%) related to ranibizumab, 42 (26.4%) to aflibercept and 11 (6.9%) to bevacizumab. For bevacizumab, all reactions are listed; for the other two medications, only the 15 most frequently recurring terms are reported.

Table 4 shows a disproportionality analysis for the intravitreal application of ranibizumab, aflibercept, and bevacizumab. Reporting odds ratio (ROR), confidence interval (CI), and p-value were calculated for each single drug compared with the other two medications considered as a unique category. For ranibizumab, only an inverse significant disproportionality (ROR <1.00) was identified in connection with retinal haemorrhage (ROR 0.14, 95% CI 0.04–0.55; p = 0.005) and uveitis (ROR 0.13, 95% CI 0.03–0.63; p = 0.012), meaning that ranibizumab probably confers less risk for these reactions as compared with aflibercept and bevacizumab. Bevacizumab showed a significant disproportionality for visual impairment (ROR

4.67, 95% CI 1.08–20.16; p = 0.04), and no other ROR showed a significant correlation with the respective data. Aflibercept showed the greatest number of significantly disproportional RORs: retinal haemorrhage (ROR 10.36, 95% CI 2.65–40.50; p <0.001), blindness (ROR 3.73, 95% CI 1.08–12.96; p = 0.04), and uveitis (ROR 6.91, 95% CI 1.64–29.13; p = 0.01) were significantly more frequently reported in association with aflibercept than with the other two VEGF inhibitors.

Discussion

A total of 8865 different reactions affecting the eye were reported within the period under consideration. The majority of cases involved adult patients and the main class of drugs associated with ocular ADRs were those acting on the nervous system. Health professionals were the main reporters of the ADRs and the majority of ICSRs pertained to patients who had ingested a single drug. A suspected relationship between drug and event was identified for half of the drug-reaction pairs (51.1%). The range between the shortest and the longest ADR was from 1 day to several years, with a median duration of about 8 days. The majority of reactions were temporary, as 4173 (47.1%) resolved completely. Visual impairment was the most commonly reported reaction and constituted 7.2% of all reported symptoms. Analysis of the association of VEGF inhibitors as a single class of drugs with ocular ADRs indicated that aflibercept was positively associated with serious ocular ADRs such as blindness, retinal haemorrhage and uveitis.

Although ADRs affecting the eye appear only in 3 of 100 patients reporting any adverse event, drug-induced ocular events are the second most common reason for official complaints against ophthalmologists [14]. Ocular ADRs primarily manifest as visual impairment, which, as an adverse side-effect of medication, is rare but can lead to considerable individual and societal burdens, and the acquisition of robust data to identify and confirm the relationship between a medication and an uncommon adverse side-effect is challenging [15]. As serious ADRs, blindness and lethal reactions constituted only a small part of the total reported ICSRs, although the real incidence of such cases

Table 3: Number and percentage of the first 15 most reported ADRs for ranibizumab, aflibercept und bevacizumab.

Ranibizumab (n = 106)			Aflibercept (n = 42)			Bevacizumab (n = 11)		
ADR	n	%	ADR	n	%	ADR	n	%
Eye pain	10	9.4%	Retinal haemorrhage	9	21.4%	Visual impairment	3	27.3%
Visual impairment	10	9.4%	Blindness	6	14.3%	Blepharitis	1	9.1%
Visual acuity reduced	7	6.6%	Uveitis	6	14.3%	Blindness transient	1	9.1%
Eye inflammation	5	4.7%	Retinal disorder	4	9.5%	Iridocyclitis	1	9.1%
Retinal disorder	5	4.7%	Retinal pigment epithelial tear	3	7.1%	Keratitis	1	9.1%
Blindness	4	3.8%	Non-infectious endophthalmitis	2	4.8%	Retinal artery embolism	1	9.1%
Retinal vein thrombosis	4	3.8%	Anterior chamber disorder	1	2.4%	Uveitis	1	9.1%
Vitreous disorder	4	3.8%	Cataract	1	2.4%	Vision blurred	1	9.1%
Vitreous floaters	4	3.8%	Eye irritation	1	2.4%	Vitreous detachment	1	9.1%
Vitreous haemorrhage	4	3.8%	Eye pain	1	2.4%			
Eye oedema	3	2.8%	Iridocyclitis	1	2.4%			
Ocular hyperaemia	3	2.8%	Photophobia	1	2.4%			
Ocular hypertension	3	2.8%	Pseudoendophthalmitis	1	2.4%			
Retinal haemorrhage	3	2.8%	Visual acuity reduced	1	2.4%			
Eye irritation	2	1.9%	Visual impairment	1	2.4%			
Total	71	67.0%	Total	39	92.9%	Total	11	100.0%

may be greater as ADRs in ophthalmology are a heterogeneous group that are not commonly detected [5]. This assumption underscores the importance of ophthalmologists' awareness of specific ocular ADRs related to systemic medication and how to detect and adequately treat these ADRs as part of good clinical practice [5].

Certain sub-populations appear to be more susceptible to ocular adverse reactions. Frail patients are more likely to be exposed to polypharmacy [16], which may increase the risk of inappropriate drug use and ADRs [17]. Our analysis supports these findings, as the percentage of serious ADRs was significantly correlated with the number of ingested medications and with patient age. A previous meta-analysis

of the relationship between systemic fluoroquinolones and retinal detachment did not show any significant association [18]. In our data we found 26 cases of retinal detachment and only one case (3.85%) was associated with the intake of fluoroquinolones, supporting the conclusion of the meta-analysis.

Interesting differences were observed with respect to drugs used to prevent angiogenesis. Our data indicate that aflibercept was positively associated with serious ocular ADRs such as blindness, retinal haemorrhage and uveitis. These results were based on very small numbers: six cases of blindness with aflibercept and four with ranibizumab (see table 3). In contrast, bevacizumab showed a signif-

Table 4: Main ADRs for ranibizumab, bevacizumab, and aflibercept, with reporting odds ratio, 95% confidence intervals, and p-value against the other two drugs.

Comparison	ADR	ROR	95% CI	p-value
Ranibizumab versus aflibercept and bevacizumab	Eye pain	5.42	0.67–43.50	0.11
	Visual impairment	1.28	0.38–4.28	0.69
	Visual acuity reduced	3.68	0.44–30.69	0.23
	Retinal disorder	0.61	0.16–2.36	0.47
	Blindness	0.45	0.15–1.36	0.16
	Vitreous floaters	2.04	0.22–18.71	0.53
	Vitreous haemorrhage	2.04	0.22–18.71	0.53
	Retinal haemorrhage	0.14	0.04–0.55	0.005
	Uveitis	0.13	0.03–0.63	0.012
	Eye irritation	1.00	0.09–11.29	1.00
	Anterior chamber disorder	0.50	0.03–8.08	0.61
	Photophobia	0.50	0.03–8.08	0.61
	Pseudoendophthalmitis	0.50	0.03–8.08	0.61
	Vitritis	0.50	0.03–8.08	0.61
	Iridocyclitis	0.16	0.00–4.10	0.27
Vision blurred	0.16	0.00–4.10	0.27	
Aflibercept versus ranibizumab and bevacizumab	Retinal haemorrhage	10.36	2.65–40.50	<0.001
	Blindness	3.73	1.08–12.96	0.04
	Uveitis	6.91	1.64–29.13	0.01
	Retinal disorder	2.36	0.60–9.24	0.22
	Anterior chamber disorder	2.83	0.17–46.28	0.47
	Eye pain	0.26	0.03–2.10	0.21
	Iridocyclitis	2.83	0.17–46.28	0.47
	Photophobia	2.83	0.17–46.28	0.47
	Pseudoendophthalmitis	2.83	0.17–46.28	0.47
	Visual acuity reduced	0.38	0.05–3.21	0.38
	Vitreous floaters	0.69	0.07–6.35	0.74
	Vitreous haemorrhage	0.69	0.07–6.35	0.74
	Vitritis	2.83	0.17–46.28	0.47
	Visual impairment	0.20	0.02–1.54	0.12
	Vision blurred	0.54	0.03–11.55	0.70
Eye irritation	0.54	0.03–11.55	0.70	
Bevacizumab versus ranibizumab and aflibercept	Visual impairment	4.67	1.08–20.16	0.04
	Blindness	1.38	0.16–11.89	0.77
	Iridocyclitis	7.30	0.61–87.57	0.12
	Uveitis	1.75	0.20–15.41	0.61
	Vision blurred	14.70	0.85–252.84	0.06
	Eye pain	0.52	0.03–9.40	0.66
	Visual acuity reduced	0.72	0.04–13.26	0.82
	Retinal disorder	0.64	0.03–11.68	0.76
	Vitreous floaters	1.13	0.06–21.82	0.93
	Vitreous haemorrhage	1.13	0.06–21.82	0.93
	Retinal haemorrhage	0.47	0.03–8.54	0.61
	Eye irritation	1.81	0.09–37.17	0.70
	Anterior chamber disorder	2.55	0.12–56.28	0.55
	Photophobia	2.55	0.13–56.28	0.55
	Pseudoendophthalmitis	2.55	0.13–56.28	0.55
Vitritis	2.55	0.13–56.28	0.55	

icant inverse association with both retinal haemorrhage and uveitis. An Australian case report on uveitis following the use of intravitreal aflibercept also cautions clinicians to be aware of late-onset sterile uveitis and vitritis after aflibercept injection [19]. Conversely, a double-blind randomised controlled trial showed that aflibercept was associated with similar visual and anatomic outcomes as ranibizumab when dosed monthly, as well as similar safety and tolerability [20].

Further research is required to investigate the culpability of VEGF inhibitors in serious eye disorders. The limited literature on this issue may be the main ascribable circumstance, but also the erroneous conduct and technique of administering intravitreal drugs may play a crucial role. One study showed that vision loss was not the result of the drug itself or the injection technique, but rather of the procedures used to prepare the syringes containing bevacizumab [21].

Pharmacovigilance studies based on spontaneous reporting have several limitations, including under- and selective reporting [22], and our findings should be interpreted in this context. Many ICSRs had missing data or data that were only partially specified; these circumstances, when applied to large datasets, can contribute to increased uncertainty surrounding the available information. Another limitation is the multiple comparison issue (the propensity to generate false positive results as the number of comparisons increases) considered endemic in the analysis of spontaneous reporting databases [23]. The voluntary nature of the reports also creates inherent limitations in data interpretation, and population differences across the participating countries have not been accounted for in the present study. In addition, clinical information contained in a spontaneous reporting database such as the WHO Vigibase is necessarily limited and cases can be reported more than once. However, our method allowed us to eliminate as many potential duplicate records as possible [8]. Finally, causality assessment was frequently not reported in the retrieved records [24].

Our findings highlight the importance of the routine detection of adverse reactions by physicians and other health professionals. Failure to recognise an ADR may result in a prescribing cascade whereby a new drug is administered to treat the adverse effect of the culprit drug, thus exposing the patient to a continued risk of an ADR from the culprit drug and additional risks from the newly prescribed drug [25]. To promote reporting of ocular ADRs, the awareness of both ophthalmologists and other practitioners of the risk of such ADRs could be increased by introducing routine pharmacovigilance activities into daily practice or by enhancing education in pharmacovigilance at both the under- and postgraduate level.

In conclusion, ocular ADRs in Switzerland may be more common than the number reported by health professionals suggests, implying that a more meticulous approach is required to detect serious ADRs. Serious adverse events are frequently overlooked because they are more common when polypharmacy is present, increasing the effort needed to determine whether a single drug is more likely to cause a specific ADR than the other medications. Although our data indicate that aflibercept was more significantly associated with serious ocular ADRs than other VEGF in-

hibitors, care is required in the use of this class of drugs because of the lack of relevant literature and risk of improper drug administration, leading to biased results.

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