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Abstract

Purpose: Drug-induced uveitis is a rare but sight-threatening condition. We seek to determine the spectrum of drug-induced uveitis at the era of immune checkpoint inhibitors (ICI).

Methods: Retrospective pharmacovigilance study based on adverse drug reactions reported within VigiBase, the WHO international pharmacovigilance database. We included deduplicated individual case safety reports (ICSRs) reported as 'uveitis' at Preferred Term level according to the Medical Dictionary for Drug Regulatory Activities between 1967 and 04/28/2019. We performed a case/non-case analysis to study if suspected drug-induced uveitis were differentially reported for each suspected treatment compared to the full database. We excluded drugs with potential indication bias.

Results: 1,404 ICSRs corresponding to 37 drugs had a significant over-reporting signal with a median age of 57 [42-68] years and 45.7% of males. We identified five major groups of treatments: bisphosphonates (26.9%), non-antiviral anti-infectious drugs (25.4%), protein kinase inhibitors (15.5%), ICI (15.0%), and antiviral drugs (11.1%). Severe visual loss was reported in 12.1% of cases. ICI and protein kinase inhibitors were the most recently emerging signals. The time to onset between first infusion and uveitis was significantly different between groups ranging from 5 days [2-19] in the bisphosphonate group to 138.5 [47.25-263.75] in protein kinase inhibitors group ($p<0.0001$). Anti-Programmed Cell death 1 represented more than 70% of ICI-induced uveitis. We identified Vogt-Koyanagi-Harada (VKH)-like syndrome as being associated with ICI use.

Conclusions: The spectrum of drug-induced uveitis has changed with the evolution of pharmacopeia and the recent emergence of ICIs. VKH-like syndrome has been reported with ICI and protein kinase inhibitors therapy.

Keywords: drug induced-adverse event, uveitis, immune checkpoint inhibitors, protein kinase inhibitors, visual loss

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Introduction

Uveitis represents one of the leading causes of visual deficit and handicap worldwide. Uveitis is defined by an inflammation of the uveal tract of the eye (including the iris, the ciliary body, and the choroid). Usually, uveitis is classified according to the location of the inflammation (anterior, intermediate, posterior or panuveitis). It is thought to be responsible for 5% of legal blindness cases, owing mainly to its complications including macular alterations, glaucoma and retinal ischemia [1]. At the 10-year follow-up, 20% of the patients suffered from some degree of visual loss [2]. The reported prevalence of uveitis varies from 24.9 cases to 52.4 cases per 100,000 person-years depending on the ethnicity [3,4]. Moreover, uveitis is more frequent in middle-aged populations though long-term visual loss is a major concern in this population. The cause of uveitis depends on several factors such as ethnicity and geographic origin, age, gender, genetic factors such as HLA-types [5], and localization of inflammatory reactions (anterior, posterior, panuveitis) [6]. While infectious causes represent the first etiology in developing countries (30-50%), non-infectious uveitis is more prevalent in the western world [5]. Despite extensive workup, 30-60% of uveitis cases remain undiagnosed.
Drug-induced uveitis represents a rare cause of uveitis, estimated at 0.3 to 0.5% of all cases [7]. Over the last decade, the spectrum of drugs inducing uveitis has evolved paralleling the evolution of pharmacopeia. In the '90s, anti-infectious treatments were the most common causal drugs including cidofovir and rifabutin [8,9]. More recently, drug-induced uveitis have been reported after the use of new anti-cancer treatments such as protein kinase inhibitors and immune checkpoint inhibitors (ICI) [10,11]. In the pivotal clinical trials of ICI, ophthalmic adverse events occurred rarely between 0.4 to 1% of patients [12]. However, only a few series of case reports have been published [11,13,14]. Having in mind the fact that the population exposed to these new drugs will be increasing, there is an urgent need for a better and systematic characterization of their adverse events.

This study aims to describe the spectrum of drug-induced uveitis using an international case safety report database. By gathering a large number of cases, we expect to obtain a more accurate picture of these adverse events.

Methods

Study design

The study is a disproportionality analysis based on adverse drug reactions (ADR) reported within VigiBase, the WHO global deduplicated database of Individual Case Safety Report (ICSR) [15]. VigiBase contains over 20,000,000 ICSRs of suspected medication ADR (as of 01/2019) submitted by national pharmacovigilance centers from more than 130 countries since 1967. These reports originate from different sources such as physicians or other healthcare professionals, pharmaceutical companies, and patients, and generally occur post-marketing.

Procedure

This observational pharmacological retrospective study included all ICSRs reported as 'uveitis' at Preferred Term level according to the Medical Dictionary for Drug Regulatory Activities (MedDRA) between 1967 and 04/28/2019. The drugs included in the analysis were reported as 'suspected' in VigiBase and we focused on the

drugs with systemic administration. Drugs with potential indication and protopathic bias were excluded from analysis and the corresponding list of excluded drugs can be found in supplementary Table 1. Each ICSR contains general administrative information (reporter qualification, date of reporting, country of origin), patient characteristics (age, sex), drugs (indication for the drug, dosage regimen, start and end dates, route of administration) and reactions/events (reported terms, MedDRA classification terms, onset date, end date, seriousness, outcome).

Statistical analysis

VigiBase allows for case/non-case analysis (disproportionality analysis) which we utilized to study if suspected drug-induced uveitis were differentially reported for each suspected treatment compared to the full database. Disproportionality is calculated by the information component (IC) when using the entire database as a comparator. Calculation of the IC, using a Bayesian confidence propagation neural network, was specifically developed and validated by Uppsala Monitoring Centre as an automated, flexible indicator value for disproportionate reporting that compares expected and observed adverse drug reactions associations to find new drug-ADR signals with identification of probability difference from the background data (full database) [16]. The statistical formula is as follows, IC = log2 ((Nobserved+0·5)/(Nexpected+0·5) where Nexpected = (Ndrug*Neffect) / Ntotal and Nexpected is the number of case reports expected for the drug-adverse effect combination; Nobserved is the actual number of case reports for the drug-adverse effect combination; Ndrug is the number of case reports for the drug, regardless of adverse effects; Neffect: the number of case reports for the adverse effect, regardless of drug; and Ntotal: the total number of case reports in the database. IC025 is the lower end of a 95% credibility interval for the IC. A positive IC025 (>0) is deemed significant [17]. Further details concerning these statistical aspects and examples of utilisations have recently been published elsewhere [18–21].

Characteristics of cases were described in terms of medians (with interquartile range) for quantitative variables, and effective and proportion for qualitative ones. Comparisons were performed using Chi2-test or Kruskal-Wallis with Dunn's post-test, when appropriate. Time to onset was compared using the Log-rank test. P-value<0.05 was deemed significant. Analyses were performed using Graphpad Prism 6 (GraphPad Software Inc., San Diego, CA, USA).

Results

The spectrum of drug-induced uveitis in Vigibase

Since 1967, uveitis has been reported at least once as an ADR for 674 suspected drugs in VigiBase, of which 111 drugs presented a significant over-reporting signal corresponding to a positive IC025 value. We extracted 1,404 ICSRs corresponding to 37 drugs with systemic administration and after excluding treatments with potential indication or protopathic biases (**Table 1**).

The ICSRs originated mostly from Europe (45.3%), and the Americas (38.2%). The majority of ICSRs were reported by healthcare professionals (88.9%, n=976/1,098). The median age was 57 years [42-68] (n=1,084/1,404), 45.7% of cases were males (n=582/1,274). A severe visual loss was reported in 12.1% of ICSRs. When reported,

the cause of death was related to malignant progression (n=7) or other drug reaction (n=6) including myocarditis, acute renal failure. The overall mortality rate was 1.7%. Over the years, we saw a switch of causal drugs. Anti-cancer drugs (ICI and protein kinase inhibitors) were the most recently emerging signals for drug-induced uveitis (p<0.001) (**Figure 1**).

Clinical characteristics depending on the drug

We identified five groups of treatments gathering the majority of the ICSRs: bisphosphonates (n=377/1,404, 26.9%), non-antiviral anti-infectious drugs (n=356/1,404, 25.4%), protein kinase inhibitors (n=217/1,404, 15.5%), ICI (n=211/1,404, 15.0%), and antiviral drugs (n=156/1,404, 11.1%). We summarized the clinical characteristics of each group in **Table 2**. We identified significant differences in terms of median age of uveitis occurrence (p<0.0001) and sex ratio (p<0.0001) between the groups. These differences may be explained by the drug indication. For instance, in the bisphosphonate group, patients were women in 81.3% of the cases with a median age of 65 years [58-73] and the principal indication of the treatment was osteoporosis. Associated ophthalmologic symptoms were poorly reported. However, we identified 19 conjunctivitis and 25 scleritis/episcleritis cases in the bisphosphonate group, whereas it was not reported in the other groups. The time to onset between first treatment administration and uveitis was significantly different between the 5 groups ranging from 5 days [2-19] in the bisphosphonate group to 138.5 days [47.25-263.75] in the protein kinase inhibitors group (p<0.0001) (**Figure 1**). Bisphosphonate-induced uveitis occurred significantly earlier than the other drug-induced uveitis in a multivariate analysis (p<0.0001). No difference was identified between the other drugs (antiviral drugs median time to onset 68 days [38-152], ICI median time to onset 76 days [28-169], non-antiviral anti-infectious drugs 136 days [49-256], and protein kinase inhibitors 138.5 days [47.25-263.75]).

Prognosis of drug-induced uveitis

Drug-induced uveitis was reported as a serious ADR in 31.8 – 58.1% of the ICSRs. A severe visual loss (defined by the terms listed in **supplementary table 2**) was reported in 5.2% of cases (n=11/211) in the ICI group, 9.7% of cases (n=21/217) in the protein kinase inhibitor group, 9.8% of cases (n=37/377) in the bisphosphonate group, 14.6% of cases (n=52/356) in the non-antiviral anti-infectious drug group, and 17.9% (n=28/156) of cases in the antiviral drug group (p=0.0005).

Focus on ICI-induced uveitis

We identified 211 ICSRs of ICI-induced uveitis. Included patients received ICI monotherapy by anti-Programmed Cell Death 1 (anti-PD1: nivolumab n=87/211, pembrolizumab n=61/211) and by anti-Cytotoxic T-Lymphocyte-Associated Antigen 4 (anti-CTLA4: ipilimumab n=30/211). Combined immunotherapy (n= 33/211) represented 15.6% of the ICSRs. ICI were almost exclusively reported as the only suspected drugs in these ICSRs (n=195/211, 92.4%). Melanoma was the main indication of ICI therapy (n=116/211, 55.0%) followed by lung and renal cancers (respectively 17.5% and 9.0%). ICI-induced uveitis was associated with other immune-related adverse events especially cutaneous (10.4%), endocrine (9.0%), neurologic (8.5%), rheumatologic (8.2%), and gastro-enterologic (7.1%) (defined by the terms listed in **supplementary table 2**).

We identified 8 cases of drug-induced Vogt-Koyanagi-Harada syndrome (VKH) with anti-cancer drugs mainly with ICI in 6 cases and a combination of dabrafenib – trametinib in the other 2 cases. The median age in these cases was 45 years [39.3-67.8]; the sex ratio female/male was 3/1. The drug indication was melanoma in 6 ICSRs, lung cancer in 1 ICSR, and 1 was unknown. In one case, a severe visual loss was reported.

Discussion

We report here the largest series of drug-induced uveitis cases with a total of 1,404 deduplicated ICSRs involving 37 different and significantly associated drugs. As expected, the profile of drugs changed overtime following the development of new treatments with the emergence of protein kinase inhibitors and ICI as the main purveyors of uveitis in recent years. Importantly, positive signals described in this study with our agnostic approach were consistent with the previously confirmed reports of drug-induced uveitis, with liability of anti-infectious agents such as rifabutin, cidofovir, and less frequently clarithromycin and moxifloxacin described in small series in the '90s [22]. Interestingly, differences in terms of demographic characteristics, time to onset and prognosis were found between drugs. These differences may reflect the characteristics of the exposed population to a specific drug according to the treatment indication. For instance, bisphosphonates are frequently used to treat osteoporosis leading to a high proportion of female patients. However, these disparities may also be due to the impairment of different pathways depending on the drugs which is reflected by the difference in terms of time to onset. The median time to onset of uveitis ranged from 5 days with bisphosphonates to 138.5 days with protein kinase inhibitors. Finally, in our study, 35 to 58% of the uveitis were considered serious adverse events and 5.2 to 17.9% of patients experienced severe visual loss defined by the MedDRA terms listed below.

The visual prognosis of drug-induced uveitis depends on the therapeutic molecule. In a prospective study, the incidence of zoledronate-induced uveitis was 1.1% with mild-moderate acute anterior uveitis except for one severe case. At the end of follow-up, no vision loss nor long-term sequelae were reported [23]. In a case series of 7 patients with ICI-induced uveitis, the uveitis presentation varies and the visual prognosis too. One case presented an irreversible visual loss despite aggressive treatment and one patient died while being treated for uveitis [11]. In our series, we found also several deaths related to other immunotoxicities or malignant progression in patients with ICI-induced uveitis. The severity and the frequency of immunotoxicities vary depending on the site and the therapeutic target [24]. Cardiovascular immunotoxicities are severe with a mortality rate of 50% in case of myocarditis. Also, ICI-induced temporal arteritis was associated with 30% of permanent blindness [18].

The pathophysiology of drug-induced uveitis is not fully understood and depends on the cellular pathway targeted by each drug. While direct toxicity has been reported for cidofovir therapy, autoimmune and immune-mediated responses are the likely causal pathways of ICI-induced uveitis. Cidofovir is a cytomegalovirus (CMV) nucleoside analog that blocks DNA polymerase and disrupts DNA replication of CMV by competitive mechanisms. The first published series reported 26-89% of cidofovir-induced uveitis occurring after 4-11 injections which is consistent with our findings in

terms of time to onset and signal detection [8,25,26]. In our study, two other classes of antiviral molecules were associated with an over-reporting signal: protease inhibitors (ritonavir, ritonavir-lopinavir, indinavir, nelfinavir, saquinavir) and nucleoside reverse transcriptase inhibitors (lamivudine, didanosine, stavudine, abacavir-lamivudine). Assessing the causality link between these drugs and the ocular toxicity remains complicated due to various confounding factors. These treatments are co-prescribed in the highly active antiretroviral therapy regimen and may be associated with other drugs such as rifabutin or cidofovir. Though, three cases of uveitis were reported under protease inhibitors treatment with in fact, an increased systemic level of rifabutin due to interaction with the highly active antiretroviral therapy [27–29].

Bisphosphonates have been reported in large retrospective cohorts as a uveitis risk factor [30]. Potential pathological mechanisms may involve the release of pro-inflammatory cytokines (TNFα, IL6) [31]. In our study, we reported a very short time to onset of uveitis after initiation of treatment which is consistent with this acute phase response mechanism.

New anti-cancer immunotherapies target the immune checkpoints CTLA-4 for ipilimumab and PD-1/PD-L1 (Programmed Cell Death Ligand 1) axis for nivolumab and pembrolizumab. By activating the lymphocytes, thereby restoring the anti-tumor immune response, these drugs may also induce a break of tolerance leading to immune-related adverse events. Case reports and small series recently reported ICI-induced uveitis amongst other inflammatory ocular toxicities such as dry eye and orbital inflammation [11,32–34]. In the largest retrospective series, uveitis was reported in 7 patients after ICI treatment (pembrolizumab n=3, nivolumab n=1, nivolumab plus ipilimumab n=2, and atezolizumab n=1) [11]. In this study, patients were treated for melanoma (n=5), lung adenocarcinoma (n=1), and colon adenocarcinoma (n=1). All cases had bilateral uveitis. Steroids controlled the inflammation in 85.7% of cases and 1 patient presented severe vision loss despite systemic steroids [11]. Other papers reported a wide spectrum of ophthalmologic immune-related adverse events ranging from dry eye to orbital inflammation [14,34]. In the literature, ICI-induced uveitis occurred after 6 to 12 weeks of treatment which is consistent with our findings (median time of 76 days) [11,33,35]. This time to onset is longer than with other severe ICI toxicities such as myocarditis or myositis which appear after 1 to 2 injections [18]. This time to onset of 3 months could be compared to the development of ocular graft versus host disease [36]. Of note, in graft versus host disease, several ocular manifestations have been reported such as dry eye, conjunctivitis, blepharitis, and less frequently uveitis with other organ involvements especially the skin [37].

We report here the largest case series of ICI-induced uveitis with 211 ICSRs. In line with the data already published, most patients received anti-PD1 treatment for melanoma. Based on the results of the clinical pivotal trials, the expected incidence of ICI induced-uveitis is less than 1% [38,39]. ICI and protein kinase inhibitors were the only drugs associated with a peculiar form of uveitis, VKH syndrome. It is a systemic inflammatory disorder combining a bilateral chronic granulomatous panuveitis with central nervous system, auditory and integumentary (alopecia, vitiligo, poliosis) manifestations [40]. In the literature, few case-reports have also reported VKH or VKH-like syndrome induced by ICI (nivolumab, pembrolizumab or ipilimumab) or by protein kinase inhibitors (vemurafenib, encorafenib, binimetinib) [41–47], although the drug-induced form of VKH syndrome sometimes lacked the

neurological, auditory or cutaneous symptoms [46,47]. Regarding the ocular symptoms, patients presented either early or late manifestations of VKH syndrome [42] and usually improved following steroids and discontinuation of immunotherapy. Interestingly, most reported patients were treated for melanoma confirming the immune-mediated pathophysiologic mechanism of uveitis during ICI therapy. It has been reported that both CD4+ and CD8+ T cells play a crucial role in the pathogenesis of the disease by the recognition of human melanocytes and melanoma antigens [48,49]. In the case of melanoma, highly ICI-activated lymphocytes mediate the anti-cancer response but also the immune-related adverse events with a major tropism for tissues or organs containing melanocytes such as the eye, hair, skin, inner ear and choroidal plexi, all of which being potentially affected in VKH syndrome. Malignant melanoma cells and normal choroidal melanocytes may share a target epitope for T-cell recognition.

The PD-L1 molecule is constitutionally expressed in the retinal pigment epithelium, corneal epithelium and endothelium [50]. In *in vitro* models, CD4+ T cell proliferation was negatively regulated by cell-to-cell contact between T cells and human corneal endothelial cells through PD-1/PD-L1 interaction [51]. Altogether, these data suggest a potential role of the PD-1/PD-L1 axis in contributing to the immune-privileged status of the eye.

This study has several limitations due to its design and the use of a declarative pharmacovigilance database. Uveitis was defined as a reported preferred term in the database and we could not review the cases to confirm the diagnosis or reassess the liability of the drug in the occurrence of uveitis. However, this worldwide database allows aggregating the largest series of drug-induced uveitis.

In conclusion, drug-induced uveitis is a rare but potentially sight-threatening adverse event. With the rapid development of ICI therapy, physicians should be aware of its specific ocular toxicity. VKH-like syndrome represents a peculiar form induced by immune checkpoint inhibitors and/or protein kinase inhibitors, particularly in the context of melanoma. Drug-induced uveitis may represent a model to understand auto-immune uveitis development and help to find new treatment targets.

Availability of data and materials: The datasets analyzed during the current study are available on Vigibase website (http://www.vigiaccess.org/). The methods used in the article, including the preferred terms and drug names are outlined in the paper.

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Table 1: List of the 37 drugs with a significant over reporting (defined by a positive IC025 value) for uveitis (n=5,500 total uveitis ICSRs) in VigiBase (n=19,414,607 total ICSRs) through 04/28/2019.

Substance	ATC	Nobserved	Nsubstance	Ncountry	IC025	Nserious (%)	Nblindness (%)	Known/Unknown
Non-antiviral anti-infectious drugs								Known
Rifabutin	J04AB04	265	1,436	21	8.01	66 (24.9)	32 (12.1)	Probable
Clarithromycin	J01FA09	74	43,156	11	2.20	31 (41.9)	9 (12.2)	Possible
Moxifloxacin	J01MA14	61	35,392	9	2.16	53 (86.9)	16 (26.2)	Possible
Ethambutol	J04AK02	29	25,852	5	1.34	8 (27.6)	5 (17.2)	Possible
Fluconazole	J02AC01	13	19,913	7	0.25	3 (23.1)	0 (0)	Possible
Trimethoprim	J01EA01	8	9,686	4	0.22	4 (50.0)	0 (0)	Probable
Antiviral drugs								Known
Cidofovir	J05AB12	83	867	11	6.48	21 (25.3)	12 (14.5)	Probable
Indinavir	J05AE02	24	7,561	4	2.58	3 (12.5)	8 (33.3)	Possible
Ritonavir	J05AE03	23	14,707	5	1.68	10 (43.5)	2 (8.7)	Possible
Stavudine	J05AF04	24	17,168	6	1.56	7 (29.2)	9 (37.5)	Possible
Lamivudine	J05AF05	28	21,322	7	1.54	10 (35.7)	15 (53.6)	Possible
Nelfinavir	J05AE04	9	3,896	4	1.47	3 (33.3)	1 (11.1)	Possible
Saquinavir	J05AE01	7	2,622	2	1.33	1 (14.3)	1 (14.3)	Possible
Didanosine	J05AF02	10	6,799	3	1.08	4 (40.0)	4 (40.0)	Possible
Lopinavir;Ritonavir	J05AR10	10	10,103	4	0.61	7 (70.0)	2 (20)	Possible
Abacavir;Lamivudine	J05AR02	5	4,792	4	0.43	4 (66.7)	0 (0)	Possible

Protein kinase inhibitors								Known / Probable
Dabrafenib	L01XE23	97	8,769	16	4.73	88 (90.7)	9 (9.3)	
Trametinib	L01XE25	77	8,809	15	4.35	73 (94.8)	7 (9.2)	
Vemurafenib	L01XE15	76	8,688	18	4.35	54 (71.1)	7 (12.3)	
Cobimetinib	L01XE38	25	1,719	11	4.07	17 (68.0)	1 (4)	
Ibrutinib	L01XE27	37	25,459	10	1.78	29 (78.4)	6 (16.2)	
Bisphosphonates								Known / Definite
Pamidronic acid	M05BA03	51	6,785	10	3.99	20 (39.2)	3 (5.9)	
Zoledronic acid	M05BA08	195	48,990	30	3.56	122 (62.6)	19 (9.5)	
Risedronic acid	M05BA07	43	12,452	12	2.97	28 (65.1)	4 (9.3)	
Alendronic acid	M05BA04	78	48,544	20	2.12	31 (39.7)	10 (12.8)	
Alendronic acid;Colecalciferol	M05BB03	12	4,788	6	1.82	3 (25.0)	1 (8.3)	
Ranelic acid	M05BX03	6	3,180	4	0.84	4 (66.7)	0 (0)	
Immune-checkpoint inhibitors								Known / Probable
Nivolumab	L01XC17	119	32,024	15	3.37	97 (81.5)	6 (5.0)	
Ipilimumab	L01XC11	62	15,530	11	3.29	58 (93.5)	3 (4.8)	
Pembrolizumab	L01XC18	63	15,954	14	3.28	56 (88.9)	4 (6.5)	
Other drugs								
Streptokinase	B01AD01	16	5,030	2	2.31	1 (6.3)	2 (12.5)	Possible
Mitomycin	L01DC03	10	3,573	2	1.77	10 (100.0)	3 (30.0)	Possible
Anastrozole	L02BG03	13	13,818	2	0.72	11 (84.6)	0 (0)	Possible
Isotretinoin	D10BA01	36	61,250	6	0.52	26 (72.2)	3 (8.3)	Possible
Vedolizumab	L04AA33	10	13,423	4	0.26	7 (70.0)	0 (0)	Possible
Topiramate	N03AX11	15	24,636	7	0.23	12 (80.0)	8 (53.3)	Possible
Alemtuzumab	L04AA34	10	13,896	8	0.21	5 (50.0)	3 (30.0)	Possible

ATC: Anatomical Therapeutic Chemical Classification

ICSR: individual case safety report

Nobserved: The total number of VigiBase ICSRs for the substance and uveitis

Nsubstance: The total number of VigiBase ICSRs for the substance

Ncountry: Total number of countries concerned by Nobserved.

IC025: lower end of a 95% credibility interval for the information component (IC)

Nserious: The number of VigiBase ICSRs classified as serious (as per Uppsala Monitoring Centre algorithm).

Nblindness: The number of VigiBase ICSRs with severe visual loss according to the definition in supplementary Table 2.

Association of these drugs with uveitis was categorized as follow:

Definite: drugs definitely inducing uveitis based on matched case–control studies;

Probable: drugs possibly inducing uveitis based on reports in cohorts;

Possible: drugs possibly inducing uveitis based on case reports (≤10 cases)

Table 2: Characteristics of individual case safety reports according to the suspected group of drugs

Global characteristics	Immune checkpoint inhibitors	Bisphosphonates	Protein kinase inhibitors	Antiviral drugs	Other anti-infectious drugs
	N=211	N=377	N=217	N=156	N=356
Age * **year, median IQR**	65 [54-71]	65 [58-73]	59 [48.75-68]	40 [35-46]	44 [35-57.5]
Sex					
Men	110/191 (57.6)	67/359 (18.7)	92/194 (47.4)	104/131 (79.4)	184/314 (58.6)
Women	81/191 (42.4)	292/359 (81.3)	102/194 (52.6)	27/131 (20.6)	130/314 (41.4)
Reporter qualification					
Health professional	186/208 (89.4)	262/292 (89.7)	191/215 (88.8)	86/88 (97.7)	218/231 (94.4)
Non-health professional	22/208 (10.6)	30/292 (10.3)	24/215 (11.2)	2/88 (2.3)	13/231 (5.6)
Country					
Africa	0/211 (0)	9/377 (2.4)	0/217 (0)	0/156 (0)	0/356 (0)
Americas	65/211 (30.8)	102/377 (27.1)	74/217 (34.1)	93/156 (59.6)	140/356 (39.3)
Asia	59/211 (28.0)	27/377 (7.2)	19/217(8.8)	6/156 (3.8)	25/356 (7.0)

Australia	7/211 (3.3)		63/377 (16.7)		3/217 (1.4)		1/156 (0.6)		8/356 (2.2)
Europe	80/211 (37.9)		176/377 (46.7)		121/217 (55.8)		56/156 (35.9)		183/356 (51.4)
Treatments									
nivolumab	87/211 (41.2)	alendronic acid	85/377 (22.5)	vemurafenib	50/217 (23.0)	cidofovir	78/156 (50.0)	rifabutin	200/356 (56.2)
pembrolizumab	61/211 (28.9)	pamidronic acid	48/377 (12.7)	dabrafenib	22/217 (10.1)	indinavir	11/156 (7.1)	clarithromycin	16/356 (4.5)
ipilimumab	30/211 (14.2)	risedronic acid	39/377 (10.3)	ibrutinib	37/217 (17.1)	ritonavir	9/156 (5.8)	moxifloxacin	58/356 (16.3)
		ranelic acid	6/377 (1.6)	other monotherapy	8 (3.7)	lamivudine	5/156 (3.2)	ethambutol	2/356 (0.6)
nivolumab + ipilimumab	32/211 (15.2)	zoledronic acid	193/377 (51.2)	dabrafenib + trametinib	71/217 (32.7)	other monotherapy	6/156 (3.8)	trimethoprim	8/356 (2.2)
pembrolizumab + ipilimumab	1/211 (0.5)	other	6/377 (1.6)	cobimetinib + vemurafenib	23/217 (10.6)	lopinavir-ritonavir	5/156 (3.2)	fluconazole	5/356 (1.4)
				other combination	6/217 (2.8)	combination	42/156 (26.9)	combination	67/356 (18.8)
Co-suspected drugs									
None	195/211 (92.4)		362/377 (96.0)		200/217 (92.2)		99/156 (63.5)		295/356 (82.9)
1 other drug	9/211 (4.3)		10/377 (2.7)		14/217 (6.5)		34/156 (21.8)		33/356 (12.9)

≥ 2 other drugs	7/211 (3.3)		5/377 (1.3)		3/217 (1.4)		23/156 (14.7)		28/356 (7.9)
Indications									
melanoma	116/211 (55.0)	osteoporosis	173/377 (45.9)	melanoma	119/217 (54.8)	HIV	28/156 (17.9)	mycobacterial infection	63/356 (17.7)
pulmonary cancer	37/211 (17.5)	cancer	25/377 (6.6)	haematology	29/217 (13.4)	CMV	5/156 (3.2)	respiratory infection	25/356 (7.0)
renal cancer	19/211 (9.0)	other bone disease	23/377 (6.1)	pulmonary cancer	6/217 (2.8)	chorioretinitis	6/156 (3.8)	sinus infection	13/356 (3.7)
other	11/211 (5.2)	prophylaxis	6/377 (1.6)	other	6/217 (2.8)	other	11/156 (7.1)	other	22/356 (6.2)
non specified malignant neoplasm	28/211 (13.3)	non specified	150/377 (39.8)	non specified	57/217 (3.2)	non specified	106/156 (68.0)	non specified	233/356 (65.4)
Time to onset									
days, median IQR	76 [28-169]		5 [2-19]		138.5 [47.25-263.75]		136 [49-256]		68 [38-152]
	n=82/211		n=186/377		n=70/217		n=49/156		n=197/356
Outcome									
Death	5/178 (2.8)		4/192 (2.1)		8/174 (4.6)		7/43 (16.3)		4/132 (3.0)
Serious event	64/178 (36.0)		61/192 (31.8)		57/174 (32.8)		25/43 (58.1)		56/132 (42.4)
Severe visual loss	11/211 (5.2)		37/377 (9.8)		21/217(9.7)		28/156 (17.9)		52/356 (14.6)

* data available: ICI n=144/211, bisphosphonates n=310/377, oncological drugs n=136/217, antiviral drugs n=122/156, other anti-infectious n=304/356

IQR: interquartile range

Figures

Figure 1. Distribution of the reported uveitis individual case safety reports (ICSRs) according to the entry date in VigiBase for the 5 main groups of drugs.

Relative frequency distribution represents the percentage of the ICSR per year of reporting for each of the 5 mains suspected groups of drugs over the total number of uveitis ICSR per group.

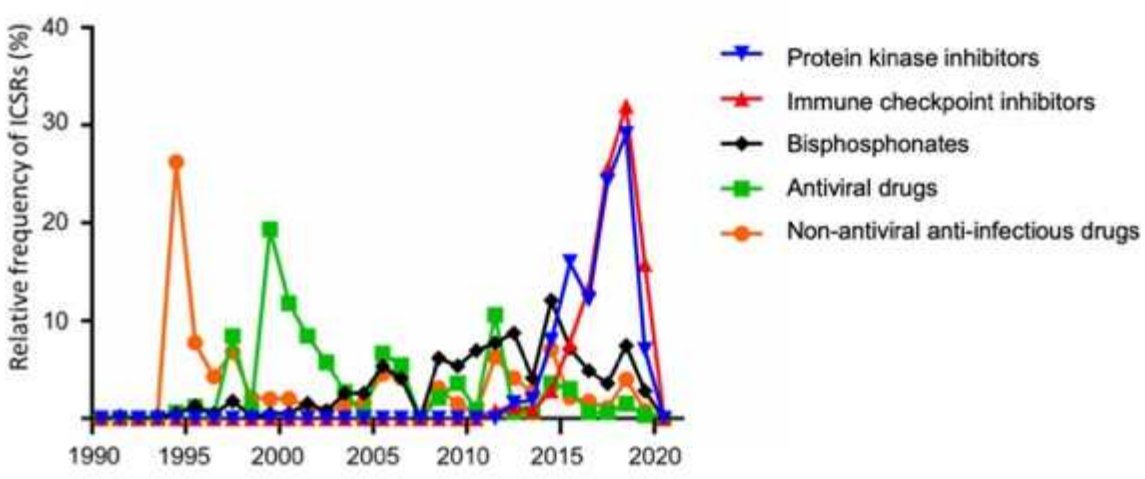

Figure 2. Time to onset for the main 5 groups of drugs. n represents the number of individual case safety reports with available time to onset data.

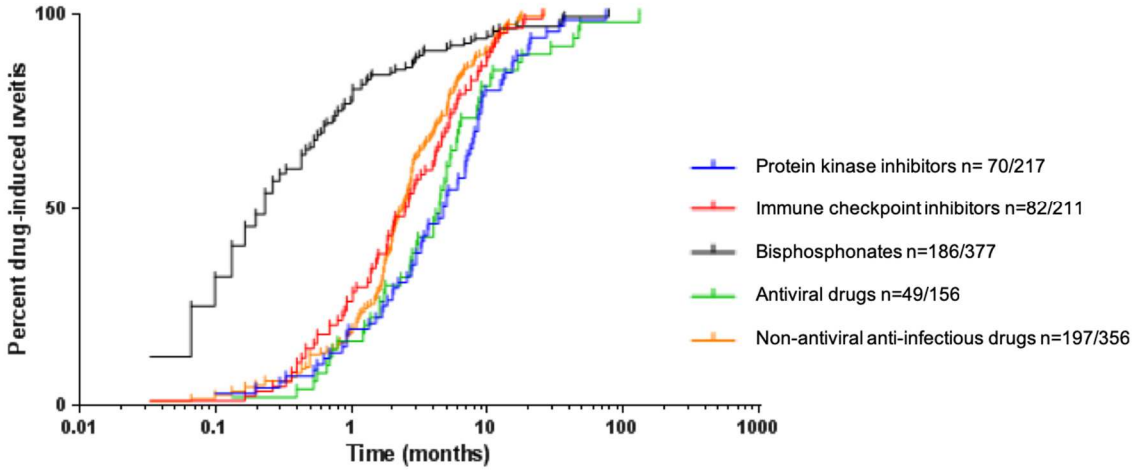

Figure 3. The overlap between the five groups of drugs identified as signals of drug-induced uveitis. Venn diagram identifying the number of uveitis cases with several suspected drugs