Review Article

Drug-induced uveitis: A review

Manisha Agarwal, Parthopratim Dutta Majumder[1], Kalpana Babu[2], Vinaya Kumar Konana[2], Mallika Goyal[3], Sara Touhami[4], Dinu Stanescu-Segall[4], Bahram Bodaghi[4]

Uveitis maybe induced by the use of various medications known as drug-induced uveitis (DIU), though rare it is an important cause of uveitis which one needs to be aware of. The drugs may be administered through any route including systemic, topical, and intravitreal. Ocular inflammation can be in the form of anterior, intermediate, posterior or pan uveitis, and rarely may present as episcleritis and scleritis. Identification of drug as the offending agent of uveitis is important as many a times stopping the drug may help recover the uveitis or the concomitant use of corticosteroids. An extensive literature review was done using the Pubmed. An overview of DIU is provided as it is important for us to be aware of this clinical entity.

Key words: Drug induced uveitis, uveitis with intravitreal drugs, uveitis with systemic drugs, uveitis with topicals, uveitis with vaccines

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_816_20

Quick Response Code:

Uveitis has a wide variety of causes. Despite significant advances in the field of diagnostics as well as in understanding the pathogenesis of uveitis, the cause of uveitis often remains unknown. Over the last few decades, drug-induced uveitis (DIU) has emerged as a rare, yet an important cause of uveitis. DIU shows extremely low prevalence (0.5%), and the data available is limited.[1] This may be due to underreporting of the cases. Various medications including vaccines administered systemically, topically or by the intravitreal route are being increasingly recognized as a cause of uveitis and/or scleritis. Ocular inflammation can be in the form of anterior, intermediate, posterior, or pan uveitis. Episcleritis, scleritis, and orbititis have also been reported.[2-4] Identification of drug as the offending agent of uveitis is important as many a times stopping the drug may help recover the uveitis or the concomitant use of corticosteroids.

Pathogenesis of DIU

Diagnosis of DIU is a challenge as no diagnostic test will help us in diagnosis, and it is not necessary that a drug that has caused uveitis in some patients will cause a similar inflammation in all of the patients who receive it.

Vitreoretina and Uveitis Services, Dr. Shroff's Charity Eye Hospital, New Delhi, [1]Department of Uveitis, Sankara Nethralaya, Chennai, Tamil Nadu, [2]Department of Uveitis and Ocular Inflammation, Vittala International Institute of Ophthalmology, Prabha Eye Clinic and Research Centre, Bangalore, Karnataka, [3]Retina-Uveitis Service, Apollo Health City, Hyderabad, Telangana, India, [4]Department of Ophthalmology, IHU FOReSIGHT, Pitié-Salpêtrière Universtiy Hospital, Paris, France

Correspondence to: Dr. Manisha Agarwal, Vitreoretina and Uveitis Services, Dr. Shroff's Charity Eye Hospital, 5027 - Kedar Nath Road, Daryaganj, New Delhi - 110 002, India. E-mail: agarwalmannii@yahoo.co.in

Received: 11-Apr-2020 Revision: 29-May-2020
Accepted: 29-May-2020 Published: 20-Aug-2020

The exact etiology of DIU remains largely unknown; however, various mechanisms have been proposed which are either direct or indirect.

Direct mechanism

Direct mechanism is when the drug has direct access to intraocular tissue. This can be in the form of topical, intravitreal, or intracameral administration. It has been hypothesized that it could be due to direct toxic effect of the drug, it's metabolite or the vehicle. This would eventually lead to breach in the blood ocular barrier, resulting in ocular inflammation.[5,6]

Indirect mechanisms

1. **Immune complex deposition in uveal tissues:** drugs can directly induce production of antibodies, and these immune complexes get deposited in the uveal tissue resulting in inflammatory reaction, e.g. Bisphosphonates.[7,8]
2. **Immune reaction to antigens released from antibiotic-induced death of microorganisms**: this happens less than 24 hours after antibiotic administration, e.g. Rifabutin.[9-11]
3. **Alteration of melanin's ability to scavenge free radicals**: drugs may combine with melanin thereby inducing uveitis and impairing the drug's effectiveness for detoxifying free radicals or by enhancing their own intrinsic uveitogenicity.[12-15] For example, the difference observed in the incidence of DIUs related to corticosteroids in blacks is 5.4% as compared to whites 0.5%.[16]

Cite this article as: Agarwal M, Dutta Majumder P, Babu K, Konana VK, Goyal M, Touhami S, *et al*. Drug-induced uveitis: A review. Indian J Ophthalmol 2020;68:1799-807.

4. **Immune check point inhibitors (ICPIs)**: tumor cells proliferate in an uncontrolled manner by activating inhibitory receptors on tumor-specific T-cells, which can downregulate and suppress T-cell function. Immune checkpoint inhibitors prevent activation of these inhibitory receptors on tumor- specific T-cells, thus enabling the T-cells to become activated and kill the tumor cells. Immune-related adverse events of ICPI are toxicities caused by nonspecific activation of the host own immune system resulting in inflammation.[17]
5. **Tumor necrotic factor (TNF) inhibitors induced reactivation of tubercular uveitis**: it has been hypothesized that neutralization of TNF by TNF inhibitors during chronic latent tuberculosis (TB) allows replication of organism within the granuloma.[18,19] TNF inhibitors can rarely cause reactivation of latent systemic TB.
6. **Other mechanisms:** oral contraceptives and topical agents, such as cholinesterase inhibitors, might induce uveitis by acting on microvasculature and causing a rupture of the blood ocular barrier.

The causal relationship between the drugs and uveitis can be graded into "definitive," "probable," "possible," and "doubtful" association based on the criteria described by Naranjo *et al*. and World Health Organization.[20,21] [Tables 1 and 2]. The maximal possible score is 13. Naranjo scores of 9 or higher imply a definite association, scores of 5 to 8 a probable association, scores of 1 to 4 a possible association, and scores of 0 make an association doubtful. The Naranjo score of various drugs and their uveitis manifestations differ [Table 3].

We may make the diagnosis of DIU by the following, though all these criteria need not be fulfilled

1. The reaction is frequently described and documented
2. Recovery of symptoms occurs when the drug is tapered or discontinued
3. Other causes for symptoms have been excluded
4. Symptoms worsen when the dose of the drug is increased
5. The adverse event is documented by objective evidence
6. Similar effects occur in a patient with similar drugs
7. Symptoms recur with re-challenge of the suspected drug

Systemic Drugs Causing Uveitis

Cidofovir is a viral DNA polymerase inhibitor used intravenously and intravitreally for treating cytomegalovirus (CMV) retinitis in HIV patients. Cidofovir is known to cause nongranulomatous anterior uveitis (43-89%) and hypotony.[22] The intrinsic ability of cidofovir with cumulative toxic effect has been postulated to be the cause of uveitis. Incidence of uveitis is more in patients on concomitant protease inhibitors, previously treated for CMV retinitis, recurrent retinitis, or immune recovery. Uveitis most commonly occurs after intravitreal injections. Davis JL *et al*. has reported a mean of 4.2 injections to cause uveitis.[22] Concomitant use of probenecid decreases the incidence of uveitis from 71% to 18% by decreasing the secretion of cidofovir from the ciliary body and decreasing the intraocular concentration.[2] Uveitis responds to topical steroids and discontinuation of the drug. Ocular hypotony is a dreaded complication due to the irreversible atrophy of the nonpigmented epithelium of ciliary body and rarely may require surgical intervention.

Rifabutin is a derivative of rifampicin and used for treating mycobacterium avium complex infection in immunocompromised patients and resistant cases of pulmonary mycobacterium TB. Rifabutin dose more than 300 mg/day causes anterior uveitis with or without hypopyon, intermediate uveitis, retinal vasculitis, or panuveitis.[23] Low body weight is a risk factor. Concomitant use of drugs like clarithromycin and ritonavir that inhibit hepatic enzymes like CYP450 and CYP3A, respectively, can increase the risk of uveitis.[24] The proposed mechanism of uveitis could be a result of dead microorganisms and toxins released or antigen-antibody immune complex mediated. Uveitis responds to topical steroids and discontinuation of the drug.

Bisphosphonates are the drugs used in the treatment of osteoporosis Paget's disease and bone metastasis. Alendronate, pamidronate, residronate and zolendronate are the nitrogenated bisphosphonates and clodronate is a non-nitrogenated bisphosphonate. Intravenous administration has greater risk. Nitrogenated bisphosphonates stimulate antigenic receptors on T lymphocytes resulting in proinflammatory mediators like interleukin-6 and tumor necrotic factor-α.[25] Uveitis develops 1-6 days after drug intake. Pamidronate is the most common bisphosphonate associated with uveitis. Uveitis responds to topical steroids, discontinuation of the drug or change to non-nitrogenated bisphosphonate[26] [Fig. 1].

Sulfonamides are used in the management of urinary tract infection and toxoplasmosis. Usually bilateral anterior uveitis develops within a week of initiation of therapy. Retinal hemorrhages have also been reported.[27] Trimethoprim usually administered with sulfamethoxazole is said to have uveitogenic property. Steven Johnson syndrome, an adverse reaction to

Table 1: The Naranjo criteria for establishing association between a medication and an adverse reaction (20)

Criteria	Yes	No	Do not know
Are there previous conclusive reports on this reaction?	1	0	0
Did the adverse reaction appear after the suspected drug was administered?	2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist administered?	1	0	0
Did the adverse reaction reappear when the drug was re-administered?	2	-1	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	2	0
Did the reaction reappear when a placebo was given?	-1	1	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was +1 decreased?	1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0
Was the adverse event confirmed by any objective evidence?	1	0	0

Total score: 0-13, 9-13: definite, 5-8: probable, 1-4: possible, 0: doubtful

sulphonamide, can rarely cause uveitis.[28] Uveitis usually responds to topical steroids.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause an immune-mediated hypersensitivity reaction in the form of tubulointerstitial nephritis and uveitis (TINU),[29] manifesting as progressive decrease in glomerular filtration rate, tubular proteinuria, and sterile pyuria. Bilateral sudden onset of acute anterior uveitis is the most common presentation though, it may present with other phenotypes. It is a diagnosis of exclusion and systemic diseases having renal and ocular inflammation such as sarcoidosis, Sjogren's syndrome, systemic lupus erythematosus, and TB should be excluded.

Table 2: Causality assessment of suspected adverse reactions (World Health Organization)

Grade of causality	Definition'
Certain causality	Where a clinical event (including a laboratory test abnormality) occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. A plausible (expected) clinical response to withdrawal of the medicine must be demonstrated and, if possible, the clinical response to restarting the medicine should also be demonstrated
Probable or likely causality	Where a clinical event occurs with a reasonable time sequence to drug administration and is unlikely to be due to any concurrent disease or other drugs or chemicals. A plausible clinical response to withdrawal of the medicine, but not to restarting the medicine, must be demonstrated
Possible causality	Where a clinical event occurs within a reasonable time sequence to drug administration but which could be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear

Mandeville *et al*.[30] in their review of 133 cases noted potential risk factors for TINU in 122 cases. Antibiotics were the commonest risk factor in 29/122, and NSAIDs were the next seen in 33 cases. Mackensen *et al*.[31] in their series of 33 cases showed NSAIDs as a cause in 9, of which 7 patients were on ibuprofen and 2/33 on antibiotics, but they concluded that none were definite drug-induced TINU. Perasaari *et al*.[32] reported that 19/31 patients had received antibiotics or NSAIDs or both, Within 2 months prior to diagnosis of TINU. Series by Li *et al*.[33] of 31 cases of TINU, prior drug usage was identified in 20/31 cases comprising of antibiotics (6/31), NSAIDs (1/31), Chinese herbs (1/31), or a combination of drugs (12/31).

Tumor necrotic factor-α inhibitors are infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol. They are used in the management of diseases like juvenile idiopathic arthritis, Crohn's disease, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, scleritis, and noninfectious uveitis.[34] Uveitis usually occurs 16-19 months after treatment and can be anterior uveitis, intermediate uveitis, posterior uveitis, scleritis, and orbital myositis.[34] Mechanism of uveitis is unknown. Etanercept has higher risk of uveitis than infliximab, and this could be secondary to up regulation of T-cell cytokine responses or the lack of induction of apoptosis.[35]

Table 3: Naranjo score and uveitis manifestations of various drugs

Name of the Drug	Route of Administration	Naranjo Score	Uveitis/Scleritis
Cidofovir	Intravenous/Intravitreal	11	Non Granulomatous Anterior Uveitis/Hypotony
Rifabutin	Oral	10	Anterior Uveitis With Hypopyon (Other Forms Also Reported)
Pamidronate	Intravenous	10	Anterior Uveitis/Scleritis/Episcleritis
Alendronate	Oral	10	Scleritis/Non Granulomatous Anterior Uveitis
Sulfonamides	Oral	10	Non Granulomatous Anterior Uveitis
Etanercept	Subcutaneous	7	Anterior/Posterior Uveitis/Periphlebitis/Chorioretinitis
Infliximab	Intravenous	7	Anterior/Posterior Uveitis/Periphlebitis/Chorioretinitis
Adalimumab	Subcutaneous	7	Anterior/Posterior Uveitis/Periphlebitis/Chorioretinitis
Fluoroquinolones	Oral	6	Anterior Uveitis (Pigment Dispersion/Ocular Hypertension)
Diethylcarbamazine	Oral	5	Anterior Uveitis/Chorioretinitis/Optic Nerve Inflammation
Metipranolol	Topical	10	Granulomatous Anterior Uveitis
Brimonidine	Topical	9	Granulomatous Anterior Uveitis/With Ocular Hypertension
Prostaglandin Analogues	Topical	9	Anterior Uveitis
Ranibizumab	Intravitreal	11	Severe Anterior Uveitis
Bevacizumab	Intravitreal	11	Anterior Uveitis
Triamcinolone Acetate	Intravitreal	7	Endophthalmitis
BCG Vaccine	Percutaneous/ Intradermal/Intravesical	9	Acute Bilateral Granulomatous/Non Granulomatous Anterior Uveitis, Panuveitis, Chorioretinitis
MMR Vaccine	Subcutaneous	7	Anterior Uveitis/Panuveitis
Influenza Vaccine	Intramuscular/ Intradermal/Nasal Spray	7	Panuveitis/APMPPE/ARN Reactivation
HBV Vaccine	Intramuscular	6	Uveitis
Varicella Vaccine	Subcutaneous	4	Anterior Uveitis, Keratouveitis, Sclerokeratitis With Anterior Uveitis/ARN

Etanercept, infliximab, and adalimumab are known to induce sarcoid-like granulomatosis.[36,37] The inverse relationship between TNF-α and interferon could affect immune cell activation, autoantibody formation, and immune complex deposition leading to an autoimmune disease.

Diethylcarbamazine (DEC) is a microfilaricide drug used as a second-line treatment for filarial infections.[38] Mazzotti reaction is the inflammatory response induced by death of the organism and is thought to be the cause of uveitis by DEC.[39] Rarely optic neuritis, retinal pigment epithelial inflammations, and chorioretinitis may occur.[40]

Topiramate is a sulfamate-substituted monosaccharide. It is used in epilepsy and migraine. The ocular adverse effects are sudden onset myopia with angle closure glaucoma.[41] Bilateral anterior uveitis and choroidal detachment have been reported.[42]

Fluoroqinolones are broad spectrum antibiotics. Moxifloxacin and ciprofloxacin are most commonly associated with ocular inflammation, whereas levofloxacin is said to have no such side effects. Iris transillumination defects, atonic pupil, and pigment dispersion with or without anterior uveitis have been reported.[43] Uveitis usually develops 0-20 days post treatment. About 50% of these patients develop raised intraocular pressure.[44] The proposed mechanism of uveitis is phototoxicity and predisposition to the autoimmune process. Patients with HLA-B27 and HLA-B51 haplotypes are more predisposed. Uveitis responds to topical steroids and drug cessation.[45] Fluoroquinolones and other antibiotics are also risk factors for TINU.[29]

Immune checkpoint inhibitors: Immune checkpoints help to prevent the immune system from attacking normal body cells and sometimes prevent T-cells from killing cancer cells. When these checkpoints are inhibited, T-cells can kill the cancer cells better. Examples of immune checkpoint proteins are programmed death-1(PD-1) on T-cells/programmed death ligand-1(PD-L1) on tumor cells, help to keep the immune response in check, thus helping tumor proliferation and CTLA-4/B7-1/B7-2. T-cells also express CD28 receptors on their surface, which triggers T-cell activation and opposes the action of CTLA-4. Activation of T-cells requires interaction between CD28 receptor and B7-1 and B7-2 ligands on antigen presenting cells. If the CTLA-4 binds with B7-1 and B7-2 ligands, T-cells are not activated. [Figs. 2 and 3]

ICPIs are monoclonal antibodies that bind to checkpoint proteins, resulting in activation of T-cells, thus causes tumor cell death. Pembrolizumab and nivolumab are monoclonal antibodies that bind to PD-1. Atezolizumab, avelumab, and durvalumab are monoclonal antibodies that bind to PD-L1 ligand on the tumor cells. Ipilimumab is a monoclonal antibody that binds to CTLA-4.[3]

Moorthy *et al*. have reported 51 patients who were on ipilimumab, nivolumab, and pembrolizumab to have uveitis 2 weeks to a year after starting ICPIs.[3]

Immune checkpoint inhibitors alone can result in proliferation of T-cells primed against antigens that have epitope similarities to uveal antigens resulting in uveitis.[46] Preponderance of ICPI- induced uveitis among patients with malignant melanoma suggests that, melanin and melanin-associated proteins that are released from lysis of melanoma cells can facilitate inflammation.[47]

Patients on nivolumab have shown a Vogt-Koyanagi Harada-like syndrome, arthritis, and rash.[48-50] Patients on

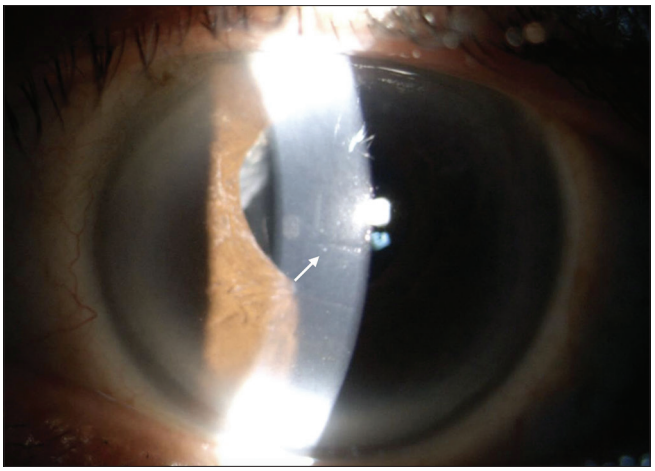

Figure 1: Anterior segment photograph showing keratic precipitates (white arrow) and descemet membrane fold in a patient receiving zolendronate

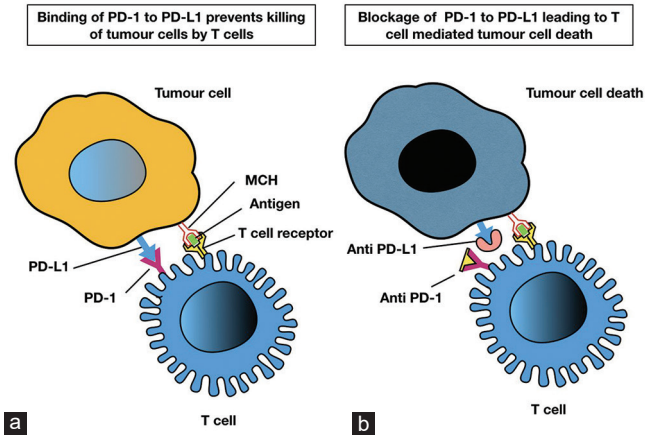

Figure 2: (a) Picture depicting how checkpoint proteins like PD-1 and PD-L1 prevent T-cell mediated tumor cell destruction. (b) anti PD-L1 and PD-1 antibodies facilitating tumor cell death

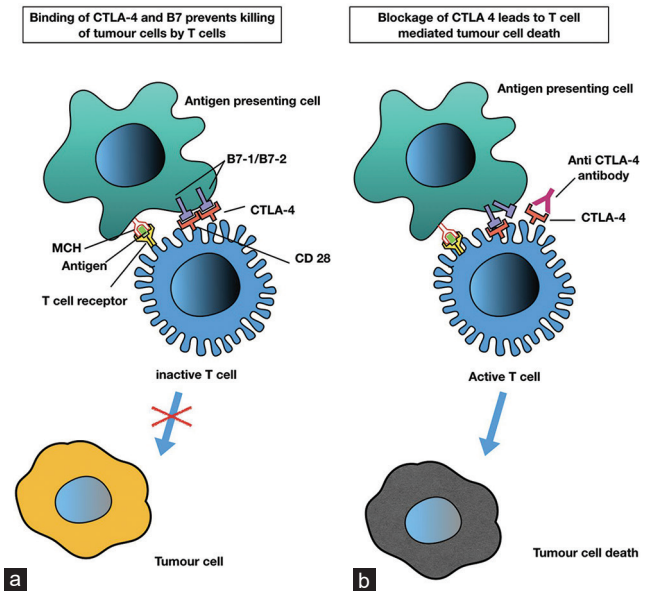

Figure 3: (a) Role of CTLA-4 in preventing T-cell-mediated tumor cell death. (b) anti-CTLA-4 antibodies facilitating T-cell-mediated tumor cell death

Pembrolizumab have developed rash, isolated vitiligo and poliosis, pulmonary sarcoidosis, colitis, and hearing loss.[51] Bilateral anterior uveitis is most commonly seen with ICPIs. There may rarely be intermediate and posterior uveitis-placoid retinal lesions, retinal vasculitis, multifocal choroiditis, or even a birdshot-like choroiditis. Mike Nguyen *et al*. have reported a case of ocular hypotony without uveitis after pembrolizumab usage in a case of advanced melanoma.[52] Uveitis associated with ICPI responds to steroids.

BRAF and MEK inhibitors: Recent advances in pathogenesis of melanoma has thrown light on the role of mitogen-activated protein kinase (MAPK) signaling disregulation and mutation in B-raf V600E gene. MEK is part of the MAPK pathway (the RAS-RAF-MEK-extracellular regulated kinase cascade). BRAF inhibitors and MEK inhibitors are being used to treat cutaneous melanomas. Vemurafenib and dabrafenib are both BRAF V600E inhibitors. Choe *et al*. reported 22 patients out of 568 patients from 4 clinical trials receiving vemurafenib who developed uveitis.[53] The uveitis was treated with topical and systemic steroids without discontinuing vemorafenib. Guedj *et al*. reported 7 patients on vemorafenib, who developed uveitis.[54] All patients in this series had bilateral uveitis and all except one patient were females. Uveitis developed after a mean period of 5.6 months after initiation of oral vemurafenib. Anterior uveitis was present in four patients, anterior and intermediate uveitis in two, and explosive panuveitis in one. All except one patient with panuveitis improved after treatment cessation. Two patients developed recurrent anterior uveitis with re-challenge.

There are isolated case reports of uveitis induced by rafenib and trametinib. Joshi *et al*. reported the development of bilateral intermediate uveitis 3 weeks after starting the first dose of both dabrafenib and trametinib, which resolved completely within 6 weeks of discontinuation of therapy without any additional corticosteroid therapy. Hence, BRAF and MEK inhibitors definitely induce uveitis.[55]

Intraocular Medications

Intravitreal triamcinolone

Triamcinolone acetonide is a long-acting, water-insoluble, crystallized corticosteroid, popularly used to treat noninfectious uveitis and macular oedema. Sterile inflammation following intravitreal administration of the drug is common and is known as sterile endophthalmitis. The reported incidence of sterile endophthalmitis varies from 0.5 to 9.7% and can occur within 1-7 days of the injection. Triamcinolone acetonide crystals can migrate to anterior chamber and form a "pseudohypopyon."[56] However, one must rule out infection following the intravitreal administration of the drug as there is formation of a locally immunosuppressed area inside the eye, which may lead to reactivation or spread of opportunistic infections. Toxic reactions are relatively uncommon with preservative-free formulations of the drug. It is not clear whether the drug, the preservative or any contaminant, is responsible for these reactions. Higher dose of the drug is found to be associated with higher incidence of noninfectious endophthalmitis.

Intravitreal Anti-Vascular Endothelial Growth Factor (Anti-VEGF)

Anti-VEGF agents such as ranibizumab (Lucentis), aflibercept (Eylea), and Bevacizumab (Avastin) off label use are being widely used in the management of various retinal pathologies such as age-related macular degeneration, diabetic retinopathy, etc., Various biosimilars are also being used for similar indications. Incidence of uveitis reported by two landmark trials (MARINA and ANCHOR) evaluating efficacy of ranibizumab was 1.3 and 0.7%, respectively.[57,58]

Sterile endophthalmitis is a dreaded complication following intravitreal administration of an anti-VEGF drug. It is characterized by significant anterior chamber and/or vitreous inflammation in the absence of infection.

Although reported mainly with bevacizumab, sterile reactions can also occur with ranibizumab. An immunogenic mechanism has been attributed owing to the larger protein load and size of bevacizumab molecule, Which makes it more immunogenic than ranibizumab.[59,60] Brolucizumab is a single-chain antibody fragment molecule, recently being used as a new anti-VEGF agent. In total, 25 cases of uveitis and 19 cases of conjunctivitis have been reported in brolucizumab-treated eyes.[61]

Topical Medication-Induced Uveitis

Metipranolol is a topical, nonselective β1/β2 blocker used in the treatment of glaucoma that reduces intraocular pressure by decreasing aqueous production. Granulomatous anterior uveitis and paradoxical increase in IOP have been reported.[62]

Betaxolol is a cardioselective [beta] 1 adrenergic receptor blocker used in the treatment of ocular hypertension and glaucoma. It causes bilateral anterior uveitis.

Brimonidine is a highly selective α2 adrenoreceptor agonist that lowers IOP by reducing aqueous production and increasing uveoscleral aqueous outflow. The most common ocular adverse events are surface allergy and conjunctival follicles. Anterior uveitis is rare and develops 11-15 months after the initiation of therapy. The uveitis may be granulomatous.[63]

Prostaglandin analogues latanoprost, travoprost, and bimatoprost are used to treat open-angle glaucoma and ocular hypertension and act via increasing uveoscleral outflow. They may cause iritis or cystoid macular edema. Granulomatous anterior uveitis has also been reported.[64]

Pilocarpine and other cholinergic drugs may cause a mild flare in the anterior chamber, posterior synechiae formation, and rarely granulomatous iridocyclitis.

Glucocorticosteroids/Corticosteroid withdrawal-associated uveitis: uveitis may occur in previously noninflamed eyes following the withdrawal of topical corticosteroids such as prednisolone acetate 1% drops, dexamethasone 0.1% drops, and triamcinolone acetonide 0.5% ointment. The incidence of uveitis in black patients (5.4%) is significantly higher than the incidence in white patients (0.5%), possibly due to the drugs combining with melanin. The mechanism for corticosteroid withdrawal induced uveitis is unknown.[16]

Vaccines Induce Uveitis

The incidence of uveitis after vaccination is reported to range from 8 to 13 in 100000 persons/year.[65] Several vaccines have been implied to cause uveitis including those against influenza, varicella zoster, diphtheria-tetanus-pertussis, bacillus Calmette-Guérin (BCG), hepatitis B, hepatitis A,

brucella, human papilloma virus (HPV), pneumococcus, and measles-mumps-rubella (MMR).[66] Before 2014, Hepatitis B vaccine (either alone or administered concurrently with other vaccines) was the leading cause of vaccine-induced uveitis, followed by HPV, Influenza, and BCG.[66] Vaccination can induce all types of uveitis, mainly transient anterior and sometimes vitritis and posterior uveitis including specific ocular syndromes such as MEWDS, APMPPE, or VKH, vasculitis, and panuveitis. Most of the patients overcome uveitis either with or without steroid therapy.[65] Permanent visual loss is rare.[65,66] Benage *et al*. have reported that the median duration of uveitis is 346 days (range: 31-686).[66]

Three mechanisms have been proposed for vaccine-induced uveitis:[67]

a. Direct infection of the ocular structures is induced by the live strain of live attenuated vaccines.[68] Guex Crosier *et al*. hypothesized that the cause of ocular inflammation after BCG vaccination might be a direct mycobacterial infection.[69] Consistent with this theory, Llorenç *et al*. showed recently in an invitro model that BCG is capable of infecting retinal pigment epithelial cells.[70] The relative efficacy of antibiotics in this context is an additional clue that corroborates this hypothesis.[67,68]
b. Adjuvants or additives (usually the aluminium salts that are used in subunit/inactivated vaccines)[71-73] may induce an immune-related vaccine associated uveitis. The so-caused autoimmune conditions are referred to as Shoenfeld syndrome and have been described after vaccines against HPV, MMR, influenza, diphtheria-tetanus-pertussis, and BCG.[66] They usually involve the presence of concurrent extraocular symptoms, such as arthralgia or myalgia, which might help in the diagnosis.
c. Molecular mimicry between the particles used for immunization and ocular structures, thereby driving the immune system to react against "the self," causing uveitis.[74]

Hepatitis B

The metanalysis published by Benage *et al*.[66] hepatitis B vaccine was found to be the leading offender for causing intraocular inflammation. In total, 40% of 289 uveitis cases were reported in association with hepatitis B vaccine, with a large majority (74 cases) reported in females. The mean age at diagnosis was 29 years (range: 1 month-58 years). The median time to uveitis onset was 23 days (range: 1 day-6 years), and the median duration of inflammation was 346 days (range: 31-686 days). In a systematic review by Fraunfelder *et al*.,[75] 32 uveitis cases were reported to have occurred after hepatitis B vaccine. The mean age of patients was 29 years (1-57 years), with a female preponderance. The mean time for onset of uveitis was 3 days (1-15 days). Interestingly, uveitis was reported to occur most frequently after the first vaccine dose in 15 patients. One patient presented with uveitis recurrence after the second and third doses. Various manifestations have been published over the years, including posterior uveitis, retinitis, VKH syndrome, and optic neuritis.[75-79]

HPV (Human Papilloma Virus)

HPV vaccination-induced uveitis is not rare (15% of 289 vaccine-associated uveitis).[66] According to Holt *et al*.[80] affected patients are young (median age of 17 years) females with a median time to onset of uveitis being 30 days.

Ocular inflammation induced by HPV vaccination theoretically affects all eye segments, including the cornea, conjunctiva, and uvea. Cases of papillitis, retinitis, Harada like serous retinal detachments and panuveitis, ampiginous choroiditis, and TINU syndrome have been described after HPV immunization.[81,82]

Influenza

There are several case reports in relation to the ocular immune reactions caused by vaccines against influenza. Various manifestations such as acute posterior multifocal placoid pigment epitheliopathy,[83,84] multiple evanescent white dot syndrome,[85] panuveitis,[86,87] exudative retinal detachment,[88] either isolated or in the context of a pseudo VKH syndrome have been reported.[89] More recently, two cases of panuveitis with orbital inflammatory syndrome were reported after influenza vaccination.[90] Williams *et al.* published the case of a 78-year-old Caucasian woman who presented with a single unilateral arterial vasculitis 8 weeks after influenza vaccination.[91] Uveitis and optic neuritis were reported in one case by Blumberg *et al*.[92] Recrudescence of a previously quiet inflammation was reported in a 77-year old female after influenza immunization, suggesting that such a vaccine might not only trigger de novo inflammatory processes but also exacerbate pre-existing inflammation.[71]

BCG: Bacille de Calmette et Guérin

Vaccination with BCG comprising of live attenuated strain of Mycobacterium Bovis has been suggested to cause uveitis in multiple reports, especially following BCG instillation for bladder cancer. In these situations, patients present with systemic symptoms e.g., arthritis and less frequently with ocular inflammatory complications such as chorioretinits, unilateral or bilateral panuveitis, and VKH-like syndrome.[93-97] Patients tend to respond favorably to corticosteroids, but recurrence is possibly associated with hypersensitivity to TB.

Measles Mumps Rubella (MMR)

Benage *et al*.[66] reported 13 uveitis cases following administration of MMR vaccine, with a female preponderance. The mean age of affected individuals was 7 years (range: 0.9-17 years), and the median time to onset of uveitis was 21 days (range: 3-145 days). Clinical presentations included anterior uveitis, panuveitis associated with dermal vasculitis, and unilateral or bilateral optic neuritis.[98,99] In an epidemiological study of 3865 patients in the US, they found that Fuchs heterochromic Iridocyclitis (FHI) was much less prevalent in patients that underwent rubella vaccination supporting the hypothesis of rubella virus in the etiology of FHI.[100]

Varicella

Varicella vaccine is a live attenuated virus that is injected subcutaneously. There are two forms of varicella vaccines. The Varivax is given at lower dose, two times in children for Varicella and Zoztavavax, which is administered once, and at a higher dose to adults to prevent Herpes Zoster. In the metanalysis published by Benage *et al*.,[66] 13 uveitis cases were reported following varicella vaccination. The mean age was 27 years (range: 4.8-86). Various manifestations are anterior uveitis, endothelitis, and kerato-uveitis.[101] One patient presented with anterior granulomatous uveitis after Shingrix vaccination made of Chinese hamster ovary cells, which could have contaminated the final vaccination product.[102] There was one report of a kerato-uveitis 8 years after vaccination in

a 16-year-old boy, but authors were unable to confirm with certainty a link with VZV vaccine.[103] There were 3 cases of acute retinal necrosis positive (age ranged from 63 to 88 years) for VZV that occurred 6–60 days after Zostavax vaccination. A 20-year-old immunosuppressed patient developed an acute retinal necrosis positive for VZV after Varivax vaccination. These patients had in common a positive PCR for the Oka strain of the varicella virus.[104]

Conclusion

DIU though rare may develop with a wide variety of topical, systemic, and intraocular medications including vaccines. A detailed drug history is therefore important in all patients with otherwise unexplained uveitis, both a new event of inflammation or a recurrence.

The onset of uveitis can be immediate or delayed by an interval that could be several months after the administration of the inciting drug.

Vaccination remains compulsory and a major priority worldwide of public health policy for a series of viral diseases and should not be interrupted or decreased because of the potential risk of vaccine-induced uveitis. The benefits of vaccines by far outweigh the risk of uveitis.

It is important to be aware of this clinical entity to avoid unnecessary investigations of the patient and also that the same drug may not cause uveitis in all of the patients. The uveitis caused by drugs usually resolves without major sequelae if prompt treatment in the form of discontinuation of the offending agent with or without the institution of steroid and cycloplegic/mydriatic therapy is done.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Fraunfelder FW, Rosenbaum JT. Drug-induced uveitis. Incidence, prevention and treatment. Drug Saf 1997;17:197-207.
2. London NJ, Garg SJ, Moorthy RS, Cunningham ET. Drug-induced uveitis. J Ophthalmic Inflamm Infect 2013;3:43-60.
3. Moorthy RS, Moorthy MS, Cunningham ET. Drug-induced uveitis. Curr Opin Ophthalmol 2018;29:588-603.
4. Cordero-Coma M, Salazar-Mendez R, Garzo-Garc I, Yilmaz T. Drug-induced uveitis. Expert Opin Drug Saf 2015;14:111-26.
5. Moorthy RS, Valluri S, Jampol LM. Drug-induced uveitis. Surv Ophthalmol 1998;42:557-70.
6. Koneru PB, Lien EJ, Koda RT. 31. Oculotoxicities of systemically administered drugs. J Ocul Pharmacol 1986;2:385-404.
7. Mader R, Narendran A, Lewtas J, Bykerk V, Goodman RC, Dickson JR, *et al*. Systemic vasculitis following influenza vaccination-report of 3 cases and literature review. J Rheumatol 1993;20:1429-31.
8. Worlledge S. Hong Kong treatment services-royal postgraduate medical school-british medical research council co-operative study of rifampicin plus ethambutol in daily and intermittent regimens. The detection of rifampicin-dependent antibodies. Scand J Respir Dis 1973;84:60-3.
9. Jacobs DS, Piliero PJ, Kuperwaser MG, Smith JA, Harris SD, Flanigan TP, *et al*. Acute uveitis associated with rifabutin use in patients with human immunodeficiency virus infection. Am J Ophthalmol 1994;118:716-22.
10. Shafran SD, Deschênes J, Miller M, Phillips P, Toma E. Uveitis and pseudojaundice during a regimen of clarithromycin, rifabutin, and ethambutol. MAC Study Group of the Canadian HIV Trials Network. N Engl J Med 1994;330:438-9.
11. Siegal FP, Eilbott D, Burger H, Gehan K, Davidson B, Kaell AT, *et al*. Dose-limiting toxicity of rifabutin in AIDS-related complex: Syndrome of arthralgia/arthritis. AIDS 1990;4:433-41.
12. D'Amato RJ, Alexander GM, Schwartzman RJ, Kitt CA, Price DL, Synder SH. Evidence for neuromelanin involvement in MPTP- induced neurotoxicity. Nature 1987;327:324-6.
13. Ings RM. The melanin binding of drugs and its implications. Drug Metab Rev 1984;15:1183-212.
14. Salazar-Bookaman MM, Wainer I, Patil PN. Relevance of drug-melanin interactions to ocular pharmacology and toxicology. J Ocul Pharmacol 1994;10:217-39.
15. Broekhuyse RM, Kuhlmann ED, Winkens HJ. Experimental autoimmune anterior uveitis (EAAU). III. Induction by immunization with purified uveal and skin melanins. Exp Eye Res 1993;56:575-83.
16. Martins JC, Wilensky JT, Asseff CF, Obstbaum SA, Buerk KM. Corticosteroid-induced uveitis. Am J Ophthalmol 1974;77:433-7.
17. Hargardon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: An overview of FDA approved immune checkpoint inhibitors. Int Immunopharmacol 2018;62:29-39.
18. Fonollosa A, Segura A, Giralt J, Garcia-Arumi J. Tuberculous uveitis after treatment with etanercept. Graefe's Arch Clin Exp Ophthalmol 2007;245:1397-9.
19. Ehlers S. Why does tumor necrosis factor targeted therapy reactivate tuberculosis? J Rheumatol Suppl 2005;74:35-39.
20. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
21. Holloway K, Green T. Drug and Therapeutics Committees: A Practical Guide. WHO Department of Essential Drugs and Medicines Policy, Geneva, Switzerland; 2003. Available from: http://apps.who.int/medicinedocs/pdf/s4882e/s4882e.pdf. [Last accessed on Feb 2020].
22. Davis JL, Taskintuna I, Freeman WR, Weinberg DV, Feuer WJ, Leonard RE. Iritis and hypotony after treatment with intravenous cidofovir for cytomegalovirus retinitis. Arch Ophthalmol 1997;115:733-7.
23. Saran BR, Maguire AM, Nichols C, Frank I, Hertle RW, Brucker AJ, *et al*. Hypopyon uveitis in patients with acquired immunodeficiency syndrome treated for systemic Mycobacterium avium complex infection with rifabutin. Arch Ophthalmol 1994;112:1159-65.
24. Shafran SD, Singer J, Zarowny DP, Deschenes J, Phillips P, Turgeon F, *et al*. Determinants of rifabutin-associated uveitis in patients treated with rifabutin, clarithromycin, and ethambutol for Mycobacterium avium complex bacteremia: A multivariate analysis. Canadian HIV Trials Network Protocol 010 Study Group. J Infect Dis 1998;177:252-5.
25. Sauty A, Pecherstorfer M, Zimmer-Roth I, Floroni P, Juillerat L, Markert M, *et al*. Interleukin-6 and tumor necrosis factor alpha levels after bisphosphonates treatment *in vitro* and in patients with malignancy. Bone 1996;18:133-9.
26. Fraunfelder FW, Fraunfelder FT. Bisphosphonates and ocular inflammation. N Engl J Med 2003;348:1187-8.
27. Kristinsson JK, Hannesson OB, Sveinsson O, Thorleifsson H. Bilateral anterior uveitis and retinal haemorrhages after administration of trimethoprim. Acta Ophthalmol Scand 1997;75:314-5.

28. Arola O, Peltonen R, Rossi T. Arthritis, uveitis, and Stevens-Johnson syndrome induced by trimethoprim. Lancet 1998;351:1102.
29. Okafor LO, Hewins P, Murray PI, Denniston AK. Tubulointerstitial nephritis and uveitis (TINU) syndrome: A systematic review of its epidemiology, demography and risk factors. Orphanet J Rare Dis 2017;12:128.
30. Mandeville JT, Levinson RD, Holland GN. The tubulointerstitial nephritis and uveitis syndrome. Surv Ophthalmol 2001;46:195-208.
31. Mackensen F, Smith JR, Rosenbaum JT. Enhanced recognition, treatment, and prognosis of tubulointerstitial nephritis and uveitis syndrome. Ophthalmology 2007;114:995-9.
32. Peräsaari J, Saarela V, Nikkilä J, Ala-Houhala M, Arikoski P, Kataja J, *et al*. HLA associations with tubulointerstitial nephritis with or without uveitis in Finnish peadiatric population: A nation-wide study. Tissue Antigens 2013;81:435-1.
33. Li C, Su T, Chu R, Li X, Yang L. Tubulointerstitial nephritis with uveitis in Chinese adults. Clin J Am Soc Nephrol 2014;9:21-8.
34. Gaujoux-Viala C, Giampietro C, Gaujoux T, Ea HK, Prati C, Orcel P, *et al*. Scleritis: A paradoxical effect of etanercept? Etanercept-associated inflammatory eye disease. J Rheumatol 2012;39:233-9.
35. Ramos-Casals M, Perez-Alvarez R, Diaz-Lagares C, Caudorado MJ, Khamashta MA. BIOGEAS Study Group. Autoimmune diseases induced by biological agents: A double-edged sword? Autoimmun Rev 2010;9:188-93.
36. Ramos-Casals M, Brito-Zeron P, Soto MJ, Caudorado MJ, Khamashta MA. Autoimmune diseases induced by TNF-targeted therapies. Best Pract Res Clin Rheumatol 2008;22:847-61.
37. Seve P, Varron L, Broussolle C, Dennis P, Kodjikian L. Sarcoid-related uveitis occurring during adalimumab therapy. Ocul Immunol Inflamm 2012;20:59-60.
38. Taylor HR, Murphy RP, Newland HS, White AT, D'Anna SA, Keyvan Larijani E, *et al*. Treatment of onchocerciasis. The ocular effects of ivermectin and diethylcarbamazine. Arch Ophthalmol 1986;104:863-7.
39. Francis H, Awadzi K, Ottesen EA. The Mazzotti reaction following treatment of onchocerciasis with diethylcarbamazine: Clinical severity as a function of infection intensity. Am J Trop Med Hyg 1985;34:529-36.
40. Bird AC, El-Sheikh H, Anderson J, Fuglsang H. Changes in visual function and in the posterior segment of the eye during treatment of onchocerciasis with diethylcarbamazine citrate. Br J Ophthalmol 1980;64:191-200.
41. Sankar PS, Pasquale LR, Grosskreutz CL. Uveal effusion and secondary angle-closure glaucoma associated with topiramate use. Arch Ophthalmol 2001;119:1210-1.
42. Dhar SK, Sharma V, Kapoor G, Seshadari KP, Chauhan VS. Topiramate induced bilateral anterior uveitis with choroidal detachment and angle closure glaucoma. Med J Armed Forces India 2015;71:88-91.
43. Eadie B, Etminan M, Mikelberg FS. Risk of uveitis with oral moxifloxacin: A comparative safety study. JAMA Ophthalmol 2015;133:81-4.
44. Willermain F, Deflorenne C, Bouffioux C, Janssens X, Koch P, Caspers L. Uveitis-like syndrome and iris transillumination after the use of oral moxifloxacin. Eye (Lond) 2010;24:1419.
45. Sandhu HS, Brucker AJ, Ma L, Vander Beek BL. Oral fluoroquinolones and the risk of uveitis. JAMA Ophthalmol 2016;134:38-43.
46. Conrady CD, Larochelle M, Pecen P, Palestine A, Shakoor A, Singh A. Checkpoint inhibitor-induced uveitis: A case series. Graefes Arch Clin Exp Ophthalmol 2018;256:187-91.
47. Dalvin LA, Shields CL, Orloff M, Sato T, Shields JA. Checkpoint inhibitor immune && therapy: Systemic indications and ophthalmic side effects. Retina 2018;38:1063-78.
48. Arai T, Harada K, Usui Y, Irisawa R, Tsuboi R. Case of acute anterior uveitis and Vogt- Koyanagi-Harada syndrome-like eruptions induced by nivolumab in a melanoma patient. J Dermatol 2017;44:975-6.
49. Matsuo T, Yamasaki O. Vogt-Koyanagi-Harada disease-like posterior uveitis in the course of nivolumab (anti-PD-1 antibody), interposed by vemurafenib (BRAF inhibitor), for metastatic cutaneous malignant melanoma. Clin Case Rep 2017;5:694-700.
50. Fujimura T, Kambayashi Y, Tanita K, Sato Y, Hidaka T, Otsuka A, *et al*. HLA-DRB1*04:05 in two cases of Vogt-Koyanagi-Harada disease-like uveitis developing from an advanced melanoma patient treated by sequential administration of nivolumab and dabrafenib/trametinib therapy. J Dermatol 2018;45:735-7.
51. Bricout M, Petre A, Amini-Adle M, Bezza W, Seve P, Kodjikian L, *et al*. Vogt-Koyanagi-Harada-like syndrome complicating pembrolizumab treatment for metastatic melanoma. J Immunother 2017;40:77-82.
52. Nguyen M, Islam M, Lim S, Sahu A, Tamjid B. Pembrolizumab induced ocular hypotony with near complete vision loss, interstitial pulmonary fibrosis and arthritis. Front Oncol 2019;9:944.
53. Choe CH, McArthur GA, Caro I, Kempen JH, Amravadi RK. Ocular toxicity in BRAF mutant cutaneous melanoma patients treated with vemurafenib. Am J Ophthalmol 2014;158:831-7.
54. Guedj M, Queant A, Funck-Brentano E, Kramkimel N, Lellouch J, Monnet D, *et al*. Uveitis in patients with late- stage cutaneous melanoma treated with vemurafenib. JAMA Ophthalmol 2014;132:1421-5.
55. Joshi L, Karydis A, Gemenetzi M, Shao EH, Taylor SR. Uveitis as a result of MAP kinase pathway inhibition. Case Rep Ophthalmol 2013;4:279-82.
56. Amato JE, Lee DH, Santos BA, Akduman AL. Steroid hypopyon following intravitreal triamcinolone acetonide injection in a pseudophakic patient. Ocul Immunol Inflamm 2005;13:245-7.
57. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, *et al*. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-31.
58. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T, *et al*. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology 2009;116:57-65.e5.
59. Hermeling S, Crommelin DJA, Schellekens H, Jiskoot W. Structure-immunogenicity relationships of therapeutic proteins. Pharm Res 2004;21:897-903.
60. Cunningham MA, Tlucek P, Folk JC, Boldt HC, Russell SR. Sequential, acute non- infectious uveitis associated with separate intravitreal injections of bevacizumab and ranibizumab. Retina Cases Brief Rep 2013;7:355-8.
61. Dugel PU, Koh A, Ogura Y, Jaffe GJ, Schmidt-Erfurth U, Brown DM, *et al*. HAWK and HARRIER: Phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology 2020;127:72-84.
62. Akingbehin T, Villada JR. Metipranolol associated granulomatous uveitis. Br J Ophthalmol 1991;75:519-23.
63. Hondeghem K, Augustinus B, De S. Bilateral granulomatous uveitis as a side effect of topical brimonidine: Two case reports. Bull Soc Belge Ophtalmol 2009;(311):51-2.
64. Packer M, Fine IH, Hoffman RS. Bilateral non-granulomatous anterior uveitis associated with bimatoprost. J Cataract Refract Surg 2003;29:2242-3.
65. Kuniyoshi K, Hatsukawa Y, Kimura S, Fujino T, Ohguro H, Nakai R, *et al*. Acute bilateral photoreceptor degeneration in an infant after vaccination against measles and rubella. JAMA Ophthalmol 2017;135:478-82.

66. Benage M, Fraunfelder FW. Vaccine-associated uveitis. Mo Med 2016;113:48-52.
67. Cunningham ET, Moorthy RS, Fraunfelder FW, Zierhut M. Vaccine-associated uveitis. Ocul Immunol Inflamm 2019;27:517-20.
68. Willis ED, Woodward M, Brown E, Popmihajlov Z, Saddier P, Annunziato PW, *et al*. Herpes zoster vaccine live: A 10 year review of post-marketing safety experience. Vaccine 2017;35:7231-9.
69. Guex-Crosier Y, Chamot L, Zografos L. Chorioretinitis induced by intravesical Bacillus Calmette-Guérin (BCG) instillations for urinary bladder carcinoma. Klin Monatsbl Augenheilkd 2003;220:193-5.
70. Llorenç V, Mesquida M, Molins B, González-Martín J, Sainz de la Maza M, Adán A. Bacillus calmette-guérin infection and cytotoxicity in the retinal pigment epithelium. Ocul Immunol Inflamm 2018;26:786-92.
71. Knopf HL. Recurrent uveitis after influenza vaccination. Ann Ophthalmol 1991;23:213-4.
72. Escott S, Tarabishy AB, Davidorf FH. Multifocal choroiditis following simultaneous hepatitis A, typhoid, and yellow fever vaccination. Clin Ophthalmol Auckl NZ 2013;7:363-5.
73. Stangos A, Zaninetti M, Petropoulos I, Baglivo E, Pournaras C. Multiple evanescent white dot syndrome following simultaneous hepatitis-A and yellow fever vaccination. Ocul Immunol Inflamm 2006;14:301-4.
74. Garip A, Diedrichs-Möhring M, Thurau SR, Deeg CA, Wildner G. Uveitis in a patient treated with Bacille-Calmette-Guérin: Possible antigenic mimicry of mycobacterial and retinal antigens. Ophthalmology 2009;116:2457-62.
75. Fraunfelder FW, Suhler EB, Fraunfelder FT. Hepatitis B vaccine and uveitis: An emerging hypothesis suggested by review of 32 case reports. Cutan Ocul Toxicol 2010;29:26-9.
76. Fried M, Conen D, Conzelmann M, Steinemann E. Uveitis after hepatitis B vaccination. Lancet Lond Engl 1987;2:631-2.
77. Sood AB, O'Keefe G, Bui D, Jain N. Vogt-Koyanagi-Harada disease associated with hepatitis B vaccination. Ocul Immunol Inflamm 2019;27:524-7.
78. Erguven M, Guven S, Akyuz U, Bilgiç O, Laloglu F. Optic neuritis following hepatitis B vaccination in a 9-year-old girl. J Chin Med Assoc JCMA 2009;72:594-7.
79. Holt HD, Hinkle DM, Falk NS, Fraunfelder FT, Fraunfelder FW. Human papilloma virus vaccine associated uveitis. Curr Drug Saf 2014;9:65-8.
80. Dansingani KK, Suzuki M, Naysan J, Samson CM, Spaide RF, Fisher YL. Panuveitis with exudative retinal detachments after vaccination against human papilloma virus. Ophthalmic Surg Lasers Imaging Retina 2015;46:967-70.
81. Khalifa YM, Monahan PM, Acharya NR. Ampiginous choroiditis following quadrivalent human papilloma virus vaccine. Br J Ophthalmol 2010;94:137-9.
82. Sawai T, Shimizu M, Sakai T, Yachie A. Tubulointerstitial nephritis and uveitis syndrome associated with human papillomavirus vaccine. J Pediatr Ophthalmol Strabismus 2016;53:190-1914.
83. Gonome T, Suzuki Y, Metoki T, Takahashi S, Nakazawa M. Acute posterior multifocal placoid pigment epitheliopathy and granulomatous uveitis following influenza vaccination. Am J Ophthalmol Case Rep 2016;4:60-3.
84. Mendrinos E, Baglivo E. Acute posterior multifocal placoid pigment epitheliopathy following influenza vaccination. Eye Lond Engl 2010;24:180-1.
85. Abou-Samra A, Tarabishy AB. Multiple evanescent white dot syndrome following intradermal influenza vaccination. Ocul Immunol Inflamm 2019;27:528-30.
86. Blanche P, Decrette C, Sicard D. Development of uveitis following vaccination for influenza. Clin Infect Dis Off Publ Infect Dis Soc Am 1994;19:979.
87. Wells MB, Garg S. Bilateral panuveitis after influenza vaccination. Retin Cases Brief Rep 2009;3:386-87.
88. Tao Y, Chang L-B, Zhao M, Li X-X. Two cases of exudative retinal detachment and uveitis following H1N1 influenza vaccination. Chin Med J (Engl) 2011;124:3838-40.
89. Kim M. Vogt-Koyanagi-Harada syndrome following influenza vaccination. Indian J Ophthalmol 2016;64:98.
90. Manusow JS, Rai A, Yeh S, Mandelcorn ED. Two cases of panuveitis with orbital inflammatory syndrome after influenza vaccination. Can J Ophthalmol 2015;50:e71-4.
91. Williams GS, Evans S, Yeo D, Al-bermani A. Retinal artery vasculitis secondary to administration of influenza vaccine. BMJ Case Rep 2015;2015:bcr2015211971.
92. Blumberg S, Bienfang D, Kantrowitz FG. A possible association between influenza vaccination and small-vessel vasculitis. Arch Intern Med 1980;140:847-8.
93. Parafita-Fernández A, Parafita MA. Bilateral iritis after vaccine for bladder cancer. Optom Vis Sci Off Publ Am Acad Optom 2015;92:e368-70.
94. Jacob M, Gambrelle J, Fleury J, Durieu I, Kodjikian L, Duquesne N, *et al*. [Panuveitis following intravesical bacille Calmette-Guerin therapy]. J Fr Ophtalmol 2006;29:552-5.
95. Hegde V, Dean F. Bilateral panuveitis and optic neuritis following Bacillus Calmette-Guérin (BCG) vaccination. Acta Paediatr Oslo Nor 1992 2005;94:635-6.
96. Uppal GS, Shah AN, Tossounis CM, Tappin MJ. Bilateral panuveitis following intravesical BCG immunotherapy for bladder carcinoma. Ocul Immunol Inflamm 2010;18292-6.
97. Loukil I, Ammari L, Hachicha F. Unilateral panuveitis following intravesical therapy with bacille of Calmette et Guerin]. Bull Soc Belge Ophtalmol. 2012;(320):23-8.
98. Sedaghat M, Zarei-Ghanavati S, Shokoohi S, Ghasemi A. Panuveitis and dermal vasculitis following MMR vaccination. East Mediterr Health J 2007;13:470-4.
99. Ferrini W, Aubert V, Balmer A, Munier FL, Abouzeid H. Anterior uveitis and cataract after rubella vaccination: A case report of a 12-month-old girl. Pediatrics 2013;132:e1035-8.
100. Suzuki J, Goto H, Komase K, Abo H, Fujii K, Otsuki N, *et al*. Rubella virus as a possible etiological agent of Fuchs heterochromic iridocyclitis. Graefes Arch Clin Exp Ophthalmol 2010;24:1487-91.
101. Hwang CW Jr, Steigleman WA, Saucedo-Sanchez E, Tuli SS. Reactivation of herpes zoster keratitis in an adult after varicella zoster vaccination. Cornea 2013;32:508-9.
102. Heydari-Kamjani M, Vante I, Uppal P, Demory Beckler M, Kesselman MM. Uveitis sarcoidosis presumably initiated after administration of shingrix vaccine. Cureus 2019;11:e4920.
103. Lin P, Yoon MK, Chiu CS. Herpes zoster keratouveitis and inflammatory ocular hypertension 8 years after varicella vaccination. Occul Immunol Inflamm 2009;17:33-5.
104. Gonzales JA, Levison AL, Stewart JM, Acharya NR, Margolis TP. Retinal necrosis following varicella-zoster vaccination. Arch Ophthalmol 2012:130:1355-6.