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REVIEW

Drug-Induced Uveitis: Patterns, Pathogenesis and Clinical Implications

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Abstract: Drug-induced uveitis is a recognized but often underdiagnosed cause of ocular inflammation, with an increasing number of systemic and topical medications implicated. The clinical presentation is highly variable, ranging from anterior to posterior uveitis, often mimicking autoimmune or infectious etiologies. This review examines the mechanisms underlying drug-induced uveitis, including immune-mediated reactions, direct toxicity, and idiosyncratic responses. A comprehensive evaluation of specific drug classes is provided, covering topical agents (prostaglandin analogues, brimonidine), intravitreal therapies (anti-VEGF agents, triamcinolone and vancomycin), antimicrobials (cidofovir, rifabutin), bisphosphonates, tumor necrosis factor (TNF) inhibitors, immune checkpoint inhibitors, BRAF and MEK inhibitors, and vaccines. For each category, the review discusses the pathogenesis, frequency of occurrence, clinical presentation, diagnostic approach and management strategies. Diagnosing drug-induced uveitis requires a high index of suspicion and a systemic drug history. A structured approach to differentiating drug-induced uveitis from other inflammatory and infectious causes is outlined, emphasizing the key clinical and imaging features that aid in diagnosis. The expanding list of medications associated with uveitis underscores the need for heightened awareness in patients presenting with ocular inflammation. Establishing causality requires a careful balance of clinical pattern recognition, temporal correlation, and structured assessment tools. Understanding the pathogenesis of drug-induced uveitis not only informs treatment decisions, including whether to discontinue or modify therapy, but also helps refine guidelines for drug safety monitoring. As novel therapies, particularly in oncology, immunomodulation and vaccination, continue to evolve, ongoing research and robust pharmacovigilance efforts will be critical in identifying risks, improving diagnostic accuracy, and optimizing patient care.

Keywords: ocular inflammation, intravitreal injections, bisphosphonates, TNF inhibitor, cancer immunotherapy, vaccines

Introduction

Uveitis, a group of inflammatory conditions affecting the uveal tract, is a significant cause of visual morbidity worldwide.[1] It is estimated to account for up to 10% of vision loss globally, disproportionately affecting individuals of working age, and placing a considerable burden on healthcare systems.[1,2] Early recognition and management of uveitis are essential to prevent complications such as cataract, glaucoma, and irreversible retinal damage.[3–5]

Among the numerous etiologies of uveitis, drug-induced uveitis is a rare but important and potentially modifiable cause. Drug-induced uveitis accounts for approximately 0.38–1.4% of all uveitis cases and is associated with a range of systemic and topical medications.[6–9] Unlike many other forms of uveitis, the risk of ongoing disease activity in drug-induced uveitis can often be mitigated through early detection and medication optimization with the prescribing physician.

Drug-induced ocular inflammation became more widely recognized in the 1990s following the use of rifabutin and cidofovir in AIDS patients.[6] In recent years, the emergence of novel intravitreal medications, immunotherapies and vaccines have led to more reports of drug-induced uveitis. Common medications implicated include systemic agents such as bisphosphonates, immune checkpoint inhibitors, antibiotics, and antiviral therapies.[7,10] Additionally, some topical agents, such as prostaglandin analogues used in glaucoma therapy, are known to provoke uveitis in susceptible

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individuals.[11] Recognizing these associations is crucial for optometrists, who often serve as the first point of contact for patients experiencing ocular symptoms.

Literature Search

A literature search was performed using the databases PubMed, MEDLINE and Google Scholar using the following search terms: "drug-induced uveitis"; "medication-induced uveitis"; "drug-induced ocular inflammation"; "vaccine-induced uveitis". Further search terms used the specific drug class and individual names in each category of medications discussed. For example, "bisphosphonate AND uveitis" and "zoledronate AND uveitis". Only English articles were included. There was no limit on the time period. Article titles and abstracts were screened. Only papers with full text available were included. Where there are multiple publications describing the same drug, review papers and larger case series were favored over single case reports.

Mechanisms of Drug-Induced Uveitis

The pathogenesis of drug-induced uveitis remains poorly understood; however, several mechanisms have been proposed, broadly categorized as direct or indirect. Direct mechanisms are hypothesized to be due to the direct toxic effect of the drug, its metabolite or the vehicle. Indirect mechanisms are due to the drug's interaction with the immune system.[10]

The inflammatory response caused by the direct mechanism is typically immediate (within 24–48 hours).[12] Drugs administered via topical, intravitreal, or intracameral routes can penetrate the ocular environment causing cytotoxicity. Likewise, systemic medications, their metabolites or excipients can cross the blood-retinal barrier (BRB) or blood-aqueous-barrier (BAB) and accumulate in ocular tissues causing toxicity and inflammation. This toxicity disrupts the integrity of the BAB and BRB, which are critical in maintaining immune privilege in the eye.[13] Damage to these barriers allows the influx of immune cells and inflammatory mediators, triggering uveitis.

Indirect mechanisms involve drug-induced modulation of the immune system, leading to inflammation mediated by cytokines, immune complexes, or activated immune cells.[10] Three main indirect pathways have been described:

1. Immune complex deposition – uveitis can occur when drugs induce production of antibodies which result in immune complexes being deposited in uveal tissues, activating the complement system and recruiting immune cells such as neutrophils and macrophages. Cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are released, amplifying the inflammatory response. This mechanism is thought to contribute to uveitis associated with bisphosphonates.[10,14]
2. Immune reaction to antigens released from antibiotic-induced death of microorganisms – uveitis may occur when antibiotics liberate antigens from dead microorganisms, which then form antigen-antibody complexes. These complexes are deposited in the uveal tissues, activating innate immune responses.[10] One example is rifabutin-associated uveitis, where the cell wall proteins of dead organisms are thought to lead to formation of antigen-antibody immune complexes.[15,16]
3. Activation of immune cells – targeted immunotherapy medications, such as immune checkpoint inhibitors, act on the immune system, causing activation of T cells which can target uveal antigens and cause drug-induced uveitis. Cytokine storms involving TNF-α, IL-17 and IL-2 have been observed in such cases, exacerbating tissue damage and barrier dysfunction.[17]

Vaccines have also been implicated in cases of uveitis.[18] Currently there are three main mechanisms proposed for vaccine-induced uveitis. The first mechanism is through direct infection of ocular structures by live-attenuated vaccines such as the herpes zoster live vaccine.[19] The second mechanism proposes adjuvants or additives used in vaccines (such as aluminum) that accumulate in uveal tissues as the trigger for inflammation.[20] The third mechanism is molecular mimicry between antigens used in the vaccine and ocular structures resulting in immune cross-reaction to uveal tissues.[20,21]

In addition to the above mechanisms, patient-level risk factors also play a major role in the development of ocular inflammation in response to a medication or a vaccine. These include genetic predisposition, pre-existing underlying autoimmune conditions, and history of uveitis. Human leukocyte antigens (HLA) have been known to be strongly

associated with uveitis, such as HLA-B27 in anterior uveitis, HLA-A29 in birdshot chorioretinopathy, HLA-B51 in Behçet's disease and HLA-DR4/B1*04 in Vogt-Koyanagi-Harada (VKH) disease.[22] It has been postulated that the presence of these HLAs can predispose to the development of drug-induced uveitis.[23]

Topical Medications

The most common topical ocular medications reported in association with drug-induced uveitis are prostaglandin analogues and brimonidine, used in glaucoma treatment.

Prostaglandin Analogues

Topical prostaglandin analogues (PGA) such as latanoprost, bimatoprost and travoprost increase uveoscleral outflow to lower intraocular pressure, and are used in management of glaucoma. There has long been concern over increased risk of uveitis and cystoid macular edema (CME) associated with topical PGA use.[24] One study estimated the rate of latanoprost-induced uveitis and CME to be 0.48% and 0.19% respectively.[11] The mechanism is thought to be due to increased breakdown in the blood-aqueous and blood-retina barrier and increased production of cytokines in the anterior chamber.[17] However, a recent large scale retrospective study of 67,517 glaucoma patients newly started on topical glaucoma therapy has drawn this into question, observing no increased risk with PGA use.[25]

Patients may present with typical symptoms of anterior uveitis, such as red eye, photophobia, blurred vision, or metamorphopsia due to CME (Figure 1). Treatment involves cessation of the medication and topical steroid drops. Careful liaison with the patient's glaucoma specialist is important to ensure that their glaucoma remains adequately monitored and controlled. In cases where the patient was rechallenged with topical latanoprost, the majority had recurrence of uveitis, but all cases were reversible with drug-cessation and treatment.[11]

Brimonidine

Brimonidine is a selective alpha-2 adrenergic agonist that reduces aqueous production and increases uveoscleral outflow. It is a common first or second line agent used in primary and secondary glaucoma. It can cause a granulomatous anterior uveitis, even years after initiation. The time of onset of brimonidine-induced uveitis is highly variable, ranging from

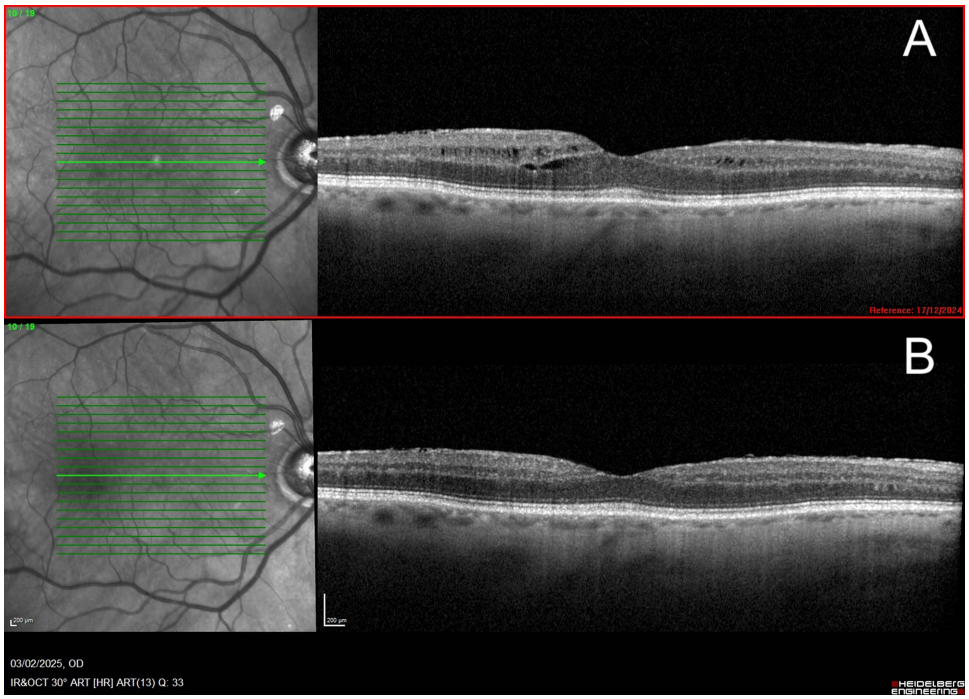

Figure 1 Latanoprost induced cystoid macular edema. (**A**) a few months after starting topical latanoprost. (**B**) resolution on cessation of latanoprost.

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a week to five years in one case series.[26] Based on the delayed onset of brimonidine-induced uveitis in most cases, it is postulated to be due to a secondary cell-mediated immune response as opposed to a direct toxic reaction.[27]

Patients with brimonidine-related uveitis classically present with acute or subacute onset of bilateral granulomatous anterior uveitis.[26] Symptoms include redness, pain, watering, photophobia and blurred vision, however patients can also be asymptomatic. Classic signs include conjunctival ciliary injection, granulomatous keratic precipitates, and anterior chamber cells and flare. It may be accompanied by raised intraocular pressure.[28] Brimonidine-related uveitis can be misdiagnosed as conjunctivitis by general practitioners without awareness of this condition, especially as it can occur after years of being on brimonidine treatment.

Assessment of the uveitis involves careful exclusion of posterior uveitis involvement and considering infectious and non-infectious differential diagnoses of granulomatous uveitis. Viral uveitis is an important differential in the presentation of hypertensive anterior uveitis. Routine uveitis screening laboratory investigations should be carried out. A chest X-ray should be performed to rule out sarcoidosis and pulmonary tuberculosis. Treatment requires cessation of brimonidine, usually with a course of topical steroids. The prognosis is good and most patients recover fully. A rechallenge typically results in uveitis recurrence.[17]

It is important to take a detailed ocular and medication history when evaluating these patients as they may fail to disclose their topical glaucoma medications. In any patient with glaucoma, it is crucial to liaise with the treating clinician before stopping a medication to ensure monitoring of intraocular pressure and timely initiation of appropriate alternative treatment.

Intravitreal Medications

Intravitreal medications are used for a variety of ocular indications. Drug-induced uveitis and sterile endophthalmitis has been reported following anti-vascular endothelial growth factor (anti-VEGF) agents, the intraocular steroid triamcinolone acetonide and the antibiotic vancomycin.

Anti-Vascular Endothelial Growth Factor

Intravitreal Anti-VEGF agents are widely used in the treatment of retinal conditions such as age-related macular degeneration (AMD) and diabetic macular edema (DME). Ranibizumab (Lucentis), aflibercept (Eylea), brolucizumab (Beovu) and faricimab (Vabysmo) have been approved by the Food and Drug Administration (FDA) for intraocular use, while bevacizumab (Avastin) has been used off-label for decades for various ophthalmic indications.[29] Anti-VEGF agents have been found to cause non-infectious intraocular inflammation, in the form of anterior uveitis, sterile endophthalmitis and retinal vasculitis. The overall incidence of post-injection intraocular inflammation mimicking endophthalmitis varies widely in the literature, ranging between 0.005% and 4.4%.[29] A retrospective review reported rates of sterile endophthalmitis following anti-VEGF injection to be 0.16%, 0.10% and 0.02% for aflibercept, bevacizumab and ranibizumab respectively.[30] Brolucizumab carries a higher risk of drug-induced uveitis of 4.6%, which includes a risk of retinal vasculitis, reported in 3.3% in the HAWK and HARRIER post hoc analyses.[31] Faricimab is the latest anti-VEGF agent to receive FDA approval for neovascular AMD and DME and has also been reported to cause uveitis.[32] At the two-year mark of the Phase 3 YOSEMITE and RHINE trials, between 0.3–1% of patients receiving faricimab developed uveitis.[33] A more recent retrospective review found the overall incidence of intraocular inflammation with faricimab to be 0.87%, with vitritis specifically observed in 0.63% of cases.[34]

Inflammation associated with intravitreal anti-VEGF injection can present with a range of clinical features. Broadly, there are two distinct presentations. The first and more common, is an acute onset sterile inflammation, which can range from subclinical anterior chamber inflammation to significant inflammation mimicking infectious endophthalmitis. The second is a delayed onset retinal vasculitis which has been described most commonly with brolucizumab but more recently also with faricimab.[31,35,36] The average time of presentation of retinal vasculitis post brolucizumab injection was reported to be 25–53 days.[31,37]

The mechanism of anti-VEGF-related intraocular inflammation may relate to patient-specific factors or medication-specific factors. Patient-specific factors include the presence of anti-drug antibodies against the anti-VEGF drug molecules, an underlying condition that leads to breakdown of the blood-ocular barrier (eg, diabetes), or previous history

of uveitis. Medication-specific risk factors include the presence of impurities and endotoxins, and the presence of the Fc antibody portion on aflibercept and bevacizumab which may trigger an immune response.[29] The mechanism for the delayed onset of retinal vasculitis following brolucizumab is most likely related to a delayed type III or type IV hypersensitivity reaction.[38,39] The timing of onset also points towards a delayed hypersensitivity reaction, where repeat exposure may result in a more rapid immune response. Baumal et al[38] observed that retinal vasculitis occurred earlier in patients who had received more than one injection of brolucizumab compared to those who had a reaction to the first injection (20 days post injection vs 35.5 days post injection, respectively).

The exact immunologic trigger for this reaction to brolucizumab and not to other anti-VEGF agents still remains unknown. The brolucizumab molecule is much smaller than the other anti-VEGFs (with a molecular weight of only 26 kDa compared with 48 kDa for ranibizumab and 115 kDa for aflibercept), and thus allows for higher molecular concentration, better tissue penetration, and a prolonged therapeutic effect.[40] This increased tissue penetration may lead to increased exposure to the immune system in eyes with a potentially compromised blood retinal barrier such as neovascular AMD and diabetes.[41]

The presentation of anti-VEGF induced uveitis is variable. It can present with acute anterior uveitis symptoms of red eye, pain, photophobia, or it can present with floaters and blurry vision without redness or pain. Differentiating sterile inflammation from infectious endophthalmitis can therefore be challenging. The timing and clinical symptoms and signs can help the clinician to differentiate the two, however, when in doubt, it is safest to treat the inflammation as infectious with an urgent vitreous tap and injection of intravitreal antibiotics and/or vitrectomy surgery.

The treatment of anti-VEGF related uveitis requires intensive topical steroids, with addition of periocular and systemic steroids depending on the extent of posterior inflammation. Most patients experience improvement with steroid treatment and regain their baseline vision. With very mild reactions, some individuals will tolerate further injections with a course of topical steroid, but most will require cessation of treatment or a switch to another agent.

The cumulative risk of endophthalmitis post intravitreal anti-VEGF injection increases with the number of injections and occurs at a higher rate earlier in the treatment course.[42] Currently, there is no data to confirm if a similar risk profile exists for sterile inflammation post anti-VEGF injection. In our literature search, we are unable to find reports on whether the risk of developing uveitis when switching to a different anti-VEGF agent is impacted by prior anti-VEGF-related uveitis. This highlights a gap in our current knowledge of drug-induced uveitis and may warrant further investigation.

Triamcinolone

Triamcinolone acetonide is a long acting, water insoluble, crystallized corticosteroid. The incidence of sterile endophthalmitis following intravitreal triamcinolone (IVTA) is reported to be between 0.20% and 6.73%.[43] This occurs less commonly with preservative-free preparations. The etiology of IVTA-induced ocular inflammation is thought to include several factors: contamination with endotoxins, direct toxic effect of preservatives within certain triamcinolone preparations, and an immune-mediated reaction to the drug or the preservatives.[43,44] Triamcinolone associated sterile endophthalmitis tend to present earlier (within 3 days), with less pain and less vision loss compared to infectious endophthalmitis.[44] Hypopyon formation is rare, and should be differentiated from a pseudohypopyon (Figure 2), which is a collection of triamcinolone crystals in the anterior chamber seen soon after IVTA in vitrectomized patients with posterior capsular defect or zonular weakness.[45] In a case of suspected sterile endophthalmitis post IVTA, it may be prudent to observe the patient closely as an inpatient with intensive topical steroid therapy to ensure that the inflammation improves within a few hours of treatment. The visual prognosis is generally good.

Vancomycin

Vancomycin is a large glycopeptide and one of the few antibiotics that is available for treatment of methicillin-resistant Staphylococcus aureus and methicillin-resistant, coagulase-negative Staphylococcus species.[46] In ophthalmic use, vancomycin can be delivered topically, intracamerally or intravitreally. Intracameral vancomycin is commonly used as part of routine phacoemulsification cataract surgery in the United States.[47]

A rare but serious adverse effect of intraocular vancomycin is hemorrhagic occlusive retinal vasculitis (HORV). The exact incidence of vancomycin-associated HORV is unreported but is thought to be exceedingly rare.[48] Our current

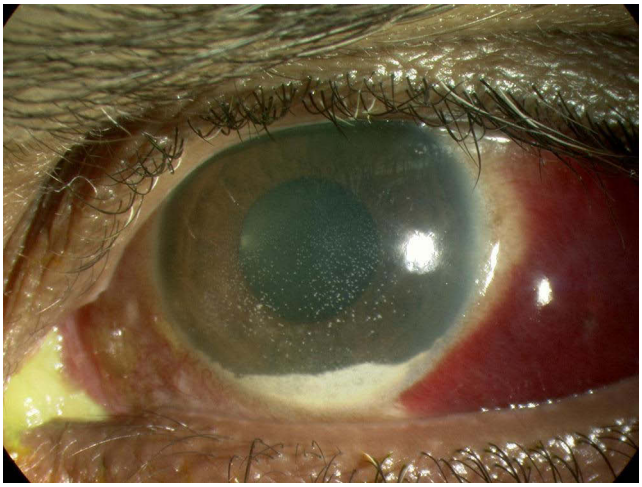

Figure 2 Pseudohypopyon formed by triamcinolone crystals in the anterior chamber.

knowledge of the condition primarily relies on a small number of case reports.[47,49–51] Patients with HORV typically present with painless blurred vision, multiple peripheral scotomas and minimal anterior segment or vitreous inflammation.[47,52] The mean time to presentation is 9 days after intraocular vancomycin.[52] Due to the relatively delayed onset, it is thought that direct toxicity is unlikely to be the main mechanism for vancomycin-associated HORV. Rather, it is postulated to be due to a type III hypersensitivity reaction where antibody–antigen complexes in vessel walls result in an inflammatory cascade.[47] Interestingly, on histological analysis of an enucleated eye, Todorich et al[50] found no evidence of leukocytoclastic vasculitis but rather marked and severe chronic non-granulomatous choroiditis accompanying necrosis of the retinal vascular network. The authors propose that the underlying pathophysiology of HORV may be a primary choroidal process with secondary effects on the retina.[50] Further studies are needed to fully understand the underlying pathophysiology of this rare drug-associated adverse reaction. Corticosteroid treatment, early panretinal laser photocoagulation, and anti-VEGF therapy are recommended for management of vancomycin-associated HORV.[52] Visual outcomes are poor and 56% of the involved eyes develop neovascular glaucoma within 1–2 months.[47]

Antimicrobials

A number of antimicrobial medications have been reported to cause uveitis. The two most well-recognized and widely reported are the antiviral cidofovir and antibiotic rifabutin.

Cidofovir

Cidofovir is a nucleoside DNA polymerase inhibitor with activity against herpes viruses. The main indication for its use is treatment of cytomegalovirus (CMV) retinitis in acquired immunodeficiency syndrome (AIDS) patients, but it is also used for non-ocular CMV infection in other immunocompromised individuals.[53] There are many case reports of systemic cidofovir inducing anterior uveitis with or without hypotony.[54–56] In patients with human immunodeficiency virus (HIV) on protease inhibitor treatment, a higher CD4+ T-lymphocyte count was associated with a higher risk of developing cidofovir-induced uveitis.[54] The pathophysiology of cidofovir-induced anterior uveitis is poorly understood, though possibly results from an intraocular accumulation of the drug through a breakdown of the BRB and a direct toxic effect on the ciliary body.[55] The average time of onset of uveitis ranged between 6–11 doses of intravenous cidofovir across several case series.[54–56] Symptoms can include red eye, pain, photophobia and blurred vision. Most cases are treated successfully with cessation of cidofovir, and a course of topical steroids and mydriatics. Rarely, the hypotony is chronic and refractory to treatment.[57]

It is important to reiterate that drug-induced uveitis is a diagnosis of exclusion. In the context of an immunocompromised person, it is important to rule out infection as a cause of the uveitis, particularly CMV. Whilst CMV will normally cause either retinitis in the immunocompromised, or hypertensive anterior uveitis in the immunocompetent, it is

unlikely to cause hypotony. Immune reconstitution uveitis may occur, particularly in those starting HIV therapy, but this usually takes longer to develop than cidofovir-induced uveitis.

Rifabutin

Rifabutin, a semi-synthetic derivative of rifampicin, is an anti-mycobacterial antibiotic used to treat mycobacterial infections including tuberculosis. It is most commonly used for Mycobacterium Avium Complex infection or prophylaxis in AIDS patients. Rifabutin is known to cause an anterior uveitis with hypopyon, and rarely intermediate uveitis, panuveitis, and retinal vasculitis.[58–62] Rifabutin-induced uveitis is dosage and duration dependent, and can occur weeks to months from initiation of the drug. Co-treatment with another drug that inhibits cytochrome P450 (a family of enzymes involved in drug metabolism) increases the risk of drug-induced uveitis.[62] The uveitis typically responds well to topical corticosteroids therapy and discontinuation of rifabutin. Like with cidofovir, in patients with AIDS, rifabutin-induced uveitis is more likely to occur when the CD4+ count is rising.[61]

Bisphosphonates

Bisphosphonates are a class of drugs derived from inorganic phosphates that are used to prevent or treat osteoporosis by reducing bone resorption by osteoclasts. They are used in age-related osteoporosis, glucocorticoid-induced osteoporosis, hypercalcemia, bone malignancy and Paget's disease. The commonly used oral forms include alendronate and risedronate. The intravenous forms include zoledronate and pamidronate. These are all nitrogen-containing bisphosphonates. Non-nitrogen containing bisphosphonates such as etidronate and clodronate are less potent and less commonly used. Both the oral and intravenous forms can cause ocular inflammation in the form of uveitis, scleritis or orbital inflammation.[63–67] Bisphosphonate-induced uveitis is the most common form of drug-induced uveitis, accounting for over two-thirds of all cases.[7]

There are several mechanisms proposed for bisphosphonate-induced ocular inflammation. Nitrogen-containing bisphosphonates are known to cause an acute phase reaction in 40% of patients due to a drug-induced release of inflammatory cytokines.[68] This reaction produces symptoms of a flu-like illness (fever, chills, muscle and bone aches), and occurs within 24–48 hours after intravenous bisphosphonate and usually resolves by 72 hours. The risk is highest with the first infusion and less likely with subsequent doses. Early onset ocular inflammation is thought to be due to a similar mechanism, with inflammation mediated by TNF-a and IL-6.[69] Other proposed mechanisms include macrophage polarization, T cell proliferation, and immune-complex deposition, which are more likely to play a part in delayed onset uveitis.[67]

Intravenous zoledronate is the most frequently reported bisphosphonate to cause ocular inflammation, likely because it is one of the most potent bisphosphonates. Figure 3 demonstrates a case of bilateral scleritis and orbital inflammation following zoledronate infusion. The estimated incidence of acute anterior uveitis after zoledronate therapy is reported to be 0.8% - 1.1% among post-menopausal women.[70,71] Ocular inflammation typically occurs within 1–7 days of intravenous administration (average 5 days) and within 15–21 days of oral administration, although late uveitis onset may occur.[7,67] Treatment involves discontinuation of the drug and topical steroids for anterior uveitis and systemic corticosteroids for scleritis and orbital inflammation. The prognosis is good, as the ocular inflammation responds well to steroid therapy.[72]

There is no consensus on restarting bisphosphonate therapy after an episode of ocular inflammation. The literature reports a mix of recurrence and no recurrence upon rechallenge with the same bisphosphonate.[7,72,73] Others report no recurrence upon switching to a different bisphosphonate or prophylactically administering corticosteroids before rechallenging with the same bisphosphonate.[67] If a rechallenge of bisphosphonate is planned, we recommend reviewing the individual within a week of treatment re-initiation to enable early identification of any adverse response and initiation of treatment.

Tumor Necrosis Factor Inhibitors

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine and the target of several biologic immunomodulatory medications. FDA approved TNF inhibitors include infliximab, adalimumab, etanercept, golimumab, and

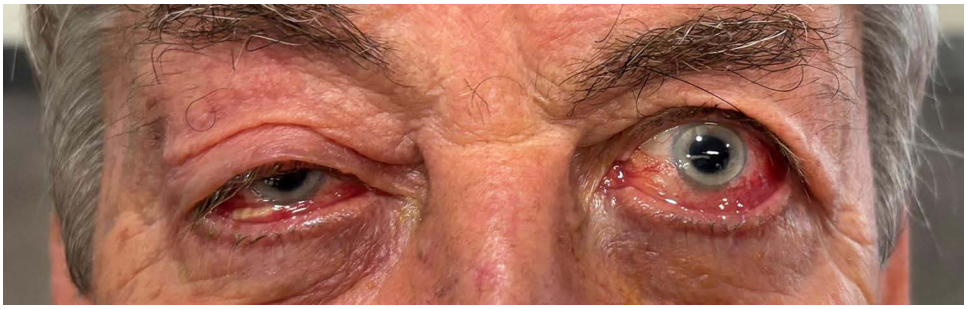

Figure 3 Bilateral scleritis and orbital inflammation after first dose of intravenous zoledronate infusion.

certrolizumab.[74] TNF inhibitors have demonstrated efficacy in many inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, inflammatory bowel disease and inflammatory eye disease.[75] While these drugs have been shown to be effective in uveitis, they can also rarely cause paradoxical worsening of preexisting uveitis or induce new onset uveitis in patients on anti-TNFs for other inflammatory conditions.[76–78] Of the abovementioned TNF inhibitors, etanercept is the most likely of this class to cause drug-induced uveitis.[79–82]

Infliximab and adalimumab are monoclonal antibodies against TNF alpha, while etanercept is a soluble TNF receptor. Infliximab and adalimumab exclusively inhibit TNF alpha, while etanercept inhibits both TNF alpha and TNF beta. These differences may partly explain the differences in their efficacy and side effect profile.[79] The mechanism behind anti-TNF induced uveitis is not well understood. It is postulated that the inverse relationship between TNF and interferon could affect immune cell activation, autoantibody formation, and immune complex deposition, leading to autoimmune disease.[83]

Non-granulomatous anterior uveitis is the most common presentation, but intermediate uveitis, cystoid macular edema (see Figure 4) and retinal vasculitis have also been reported.[79,80] There are also reports of drug-induced sarcoid uveitis following TNF inhibitor therapy.[84] The time from drug exposure to onset of uveitis is variable, ranging from days to years, averaging 12–13 months in one series and 19.5 months in another.[79,80] However, there have been reports of new-onset uveitis within days to weeks of starting a TNF inhibitor.[85] Wendling et al[80] conducted a literature review of new-onset uveitis in patients receiving TNF inhibitors and found that etanercept was the most frequently implicated agent (84.3%), followed by infliximab (12.4%) and adalimumab (3.3%). The inflammatory condition being treated was most commonly ankylosing spondylitis (72%), followed by juvenile idiopathic arthritis (11%), rheumatoid arthritis (10%), and

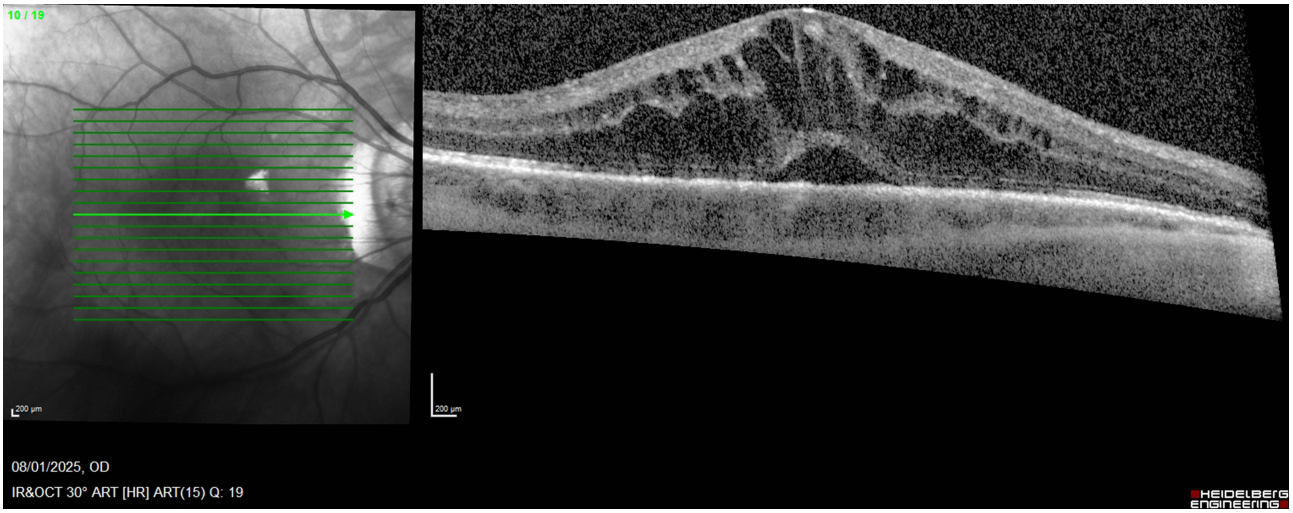

Figure 4 New onset of cystoid macular edema in a patient with history of HLA-B27 anterior uveitis on etanercept for psoriatic arthritis.

psoriatic arthritis (6%).[80] Lie et al[81] found a fourfold increase in the risk of anterior uveitis in patients with ankylosing spondylitis on etanercept compared with adalimumab, and a twofold increase for etanercept compared with infliximab.[81]

It is important to rule out infectious causes of uveitis in these immunosuppressed individuals, in particular tuberculosis (Tb). TNF inhibitors increases the risk of Tb infection or reactivation, as TNF alpha is thought to play a crucial role in the immune system's defense against tuberculosis infection.[86] New onset ocular Tb has been reported in patients on anti-TNF therapy for ankylosing spondylitis, Behcet's disease and Crohn's disease.[87,88] Clinicians should be aware of the increased risk of Tb infection or reactivation in patients on anti-TNF drugs, even with previous negative Tb screening tests. Patients who develop new onset uveitis during treatment should be reinvestigated for Tb, particularly if the pattern of uveitis does not match the known inflammatory condition they are being treated for. TNF inhibitor induced uveitis should not be diagnosed without ruling out other etiologies.

Most reported cases responded well to topical steroid treatment and discontinuation of the TNF inhibitor, but sometimes required addition of systemic and/or periocular steroid. In those with an inflammatory condition associated with uveitis (such as ankylosing spondylitis, psoriatic arthritis and Crohn's disease), a switch from etanercept to infliximab or adalimumab is usually able to control both the systemic and ocular disease. If etanercept is causing new onset of uveitis, or increased flare-ups of pre-existing uveitis, a discussion should be had between the patient's ophthalmologist or optometrist and rheumatologist regarding switching the anti-TNF agent.

Targeted Cancer Immunotherapies

Targeted cancer immunotherapies, such as immune checkpoint inhibitors and BRAF/MEK inhibitors, represent an important group of drugs increasingly recognized as potential causes of uveitis. Cancer immunotherapies work by improving the ability of the body to generate an immune response to tumor cells. In doing so, the anti-cancer drug can also cause immune-related adverse events, including uveitis.[89]

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies used in various malignancies including metastatic melanoma, small cell and non-small cell lung cancer, renal cell carcinoma and Hodgkin's lymphoma.[90] To escape the immune system, tumor cells over-express immunosuppressive molecules which reduces anti-tumor T cell function. ICIs block these immunosuppressive molecules and reactivate the cytotoxic T cells. There are three main types of checkpoint inhibitors, classified by the ligand it targets: programmed cell death 1 (PD-1) inhibitors (nivolumab, pembrolizumab, and cemiplimab), programmed cell death ligand 1 (PD-L1) inhibitors (atezolimumab, durvalumab and avelumab), and cytotoxic T lymphocyte associated protein 4 (CTLA4) inhibitors (ipilimumab).[90]

Uveitis occurs in about 1% of patients commenced on an ICI, with anterior uveitis being the most common, followed by posterior uveitis and panuveitis.[91–93] A VKH disease like presentation with multifocal serous retinal detachments is the most common form of posterior/panuveitis reported with ICIs.[94,95] Isolated intermediate uveitis is rare.[96] Ipilimumab (CTLA-4 inhibitor) was associated with the highest incidence of uveitis among ICIs, but VKH-like uveitis was most associated with PD1/PD-L1 inhibitors.[97] Uveitis occurred most commonly in patients being treated for cutaneous melanoma.[94] In one study, melanoma patients were 6.45 times more likely to develop uveitis in the first year of ICI therapy compared to non-melanoma patients.[97] Reported cases of uveitis developed between 2 weeks and 2 years after starting ICI, with a median of 9 weeks and the majority presenting within 6 months.[94,96,98] Individuals with a history of uveitis who receive ICI therapy are at increased risk of uveitis recurrence.[99] Braun et al[97] reported 38.9% of patients with a known history of anterior uveitis experienced flare-ups on ICI treatment, while those with recorded past intermediate, posterior, or panuveitis had a combined recurrence rate of 51.1%.[97]

The pathogenesis of ICI-induced uveitis is unclear. The activation of T cells may result in increased immune activity against uveal antigens. The preponderance of ICI-induced uveitis in patients treated for cutaneous melanoma suggests that there is an association between lysis of melanoma cells and T cell mediated immune activity against uveal melanin.[100] Other proposed mechanisms include activation of the complement cascade and loss of immune privilege.[101]

Patients may present with a variety of symptoms including painful red eye with photophobia, or reduced vision without pain. The presentation of uveitis is bilateral in 90%.[96] It is important to differentiate a drug related reaction from

a cancer-related process such as a paraneoplastic syndrome (eg, melanoma-associated retinopathy) or ocular metastasis. Careful dilated examination and multi-modal imaging should be conducted in all patients suspected of uveitis who are on cancer treatment with particular attention to excluding ocular metastases.[102] Figure 5 shows an ultra-widefield fundus image of ocular metastases from lung cancer.

The management of ICI-related uveitis depends on the severity of the ocular inflammation and the balance of risk and benefit of continuation of the drug. When possible, local corticosteroids are preferred over systemic corticosteroids as the impact of systemic immunosuppression on immunotherapy efficacy and tumor progression is not completely understood. If systemic steroids are used, the American Society of Clinical Oncology (ASCO) guidelines recommend that ICIs are withheld until the patient is either off all steroids or is receiving a daily dose of 10 mg oral prednisolone (or equivalent) or less.[93] The decision to discontinue an ICI should be made in collaboration with both the patient and their oncologist. Due to the low incidence of ocular adverse effects, we do not routinely screen these patients for uveitis, but all individuals on ICIs should be made aware of the risk of uveitis and symptoms to look out for.

V-Raf Murine Sarcoma Viral Oncogene Homologue B (BRAF) Inhibitors and Mitogen-Activated Protein Kinase (MEK) Inhibitors

BRAF inhibitors and MEK inhibitors are small molecule protein kinase inhibitors used to treat metastatic melanoma in patients with mutation of the BRAF gene. The BRAF mutation results in increased kinase activity which mediates cellular responses to growth signals. BRAF inhibitors specifically target mutated BRAF proteins, which are abnormally active and drive uncontrolled cell proliferation.[103] MEK inhibitors inhibit MEK1 and MEK2 downstream of BRAF in the mitogen-activated protein kinase (MAPK) signaling pathway and can be an alternative to BRAF inhibitors in patients that develop resistance. MEK inhibitors are frequently used in combination with BRAF inhibitors to counteract acquired resistance during BRAF inhibitor monotherapy.[104]

FDA approved BRAF inhibitors include vemurafenib, dabrafenib and encorafenib. MEK inhibitors include trametinib, cobimetinib and binimetinib.[105] These targeted therapies have revolutionized the treatment of unresectable BRAF-mutant metastatic melanoma, and significantly improved the survival rate. However, with their increasing use, there is also increasing reporting of ocular adverse events associated with BRAF and MEK inhibitors. The incidence of uveitis associated with BRAF inhibitor use ranges from 1–4%.[106] In a cohort study by Dimitriou et al[104] involving patients with advanced melanoma treated with either ICI or BRAF/MEK inhibitors, 1.3% of patients in the ICI group and 3.8% in the

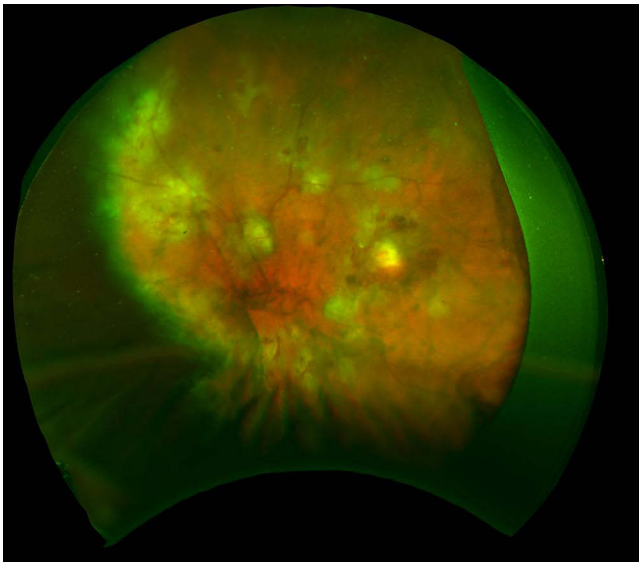

Figure 5 Ocular metastases from small cell lung cancer.

BRAF/MEK inhibitor group developed uveitis.[104] Figures 6 and 7 depicts a case of BRAF inhibitor associated panuveitis with multifocal choroiditis appearance on indocyanine green angiogram.

A national medical claims-based study in South Korea reviewed 77,323 patients with cutaneous melanoma or lung cancer who received BRAF inhibitor therapy, ICI therapy or conventional cytotoxic chemotherapy only. They found the one-year cumulative incidence of uveitis was 0.33% in the conventional group, 0.35% in the ICI group, and 2.27% in the BRAF inhibitor group. They also found the uveitis risk increased 3.71-fold after BRAF-inhibitor exposure. Most cases occurred within 160 days after drug administration.[107]

The mechanism driving BRAF/MEK inhibitor induced uveitis has not been fully elucidated. It has been postulated that MAPK inhibition might trigger the production of reactive oxygen species, leading to the breakdown of the BRB and subsequent loss of the immune-privileged ocular site. This could potentially initiate an autoimmune response, resulting in uveitis. Another accepted mechanism for uveitis in patients with melanoma is the autoimmunity against antigens shared between melanoma cells and melanocytes of the choroid, similar to ICI-associated uveitis.[106]

Like ICI-associated uveitis, the uveitis location is most commonly anterior uveitis.[23,103] There are also reported cases of VKH-like panuveitis related to BRAF/MEK inhibitors in melanoma patients, and it is suggested that individuals with HLA-DRB1*04 detected is predisposed to this VKH-like inflammatory response to BRAF/MEK inhibitors.[23]

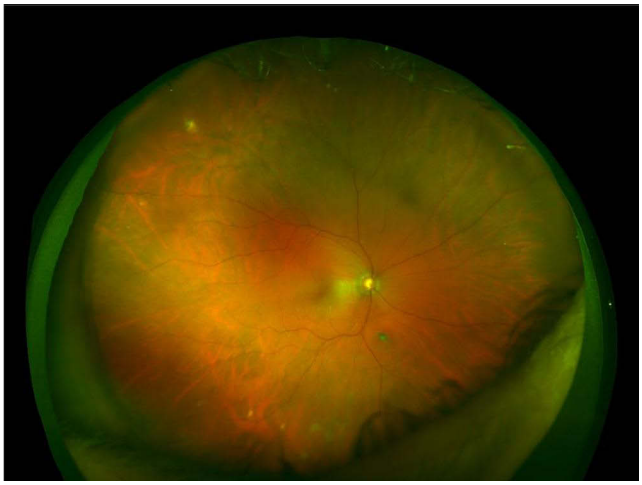

Figure 6 Bilateral panuveitis in a patient on BRAF inhibitor dabrafenib for metastatic melanoma.

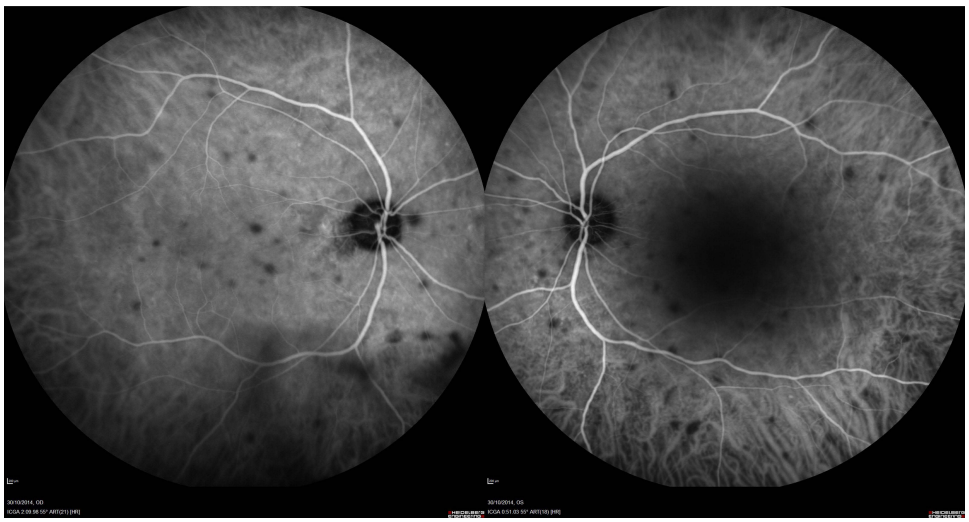

Figure 7 Indocyanine green angiogram of bilateral BRAF inhibitor induced panuveitis.

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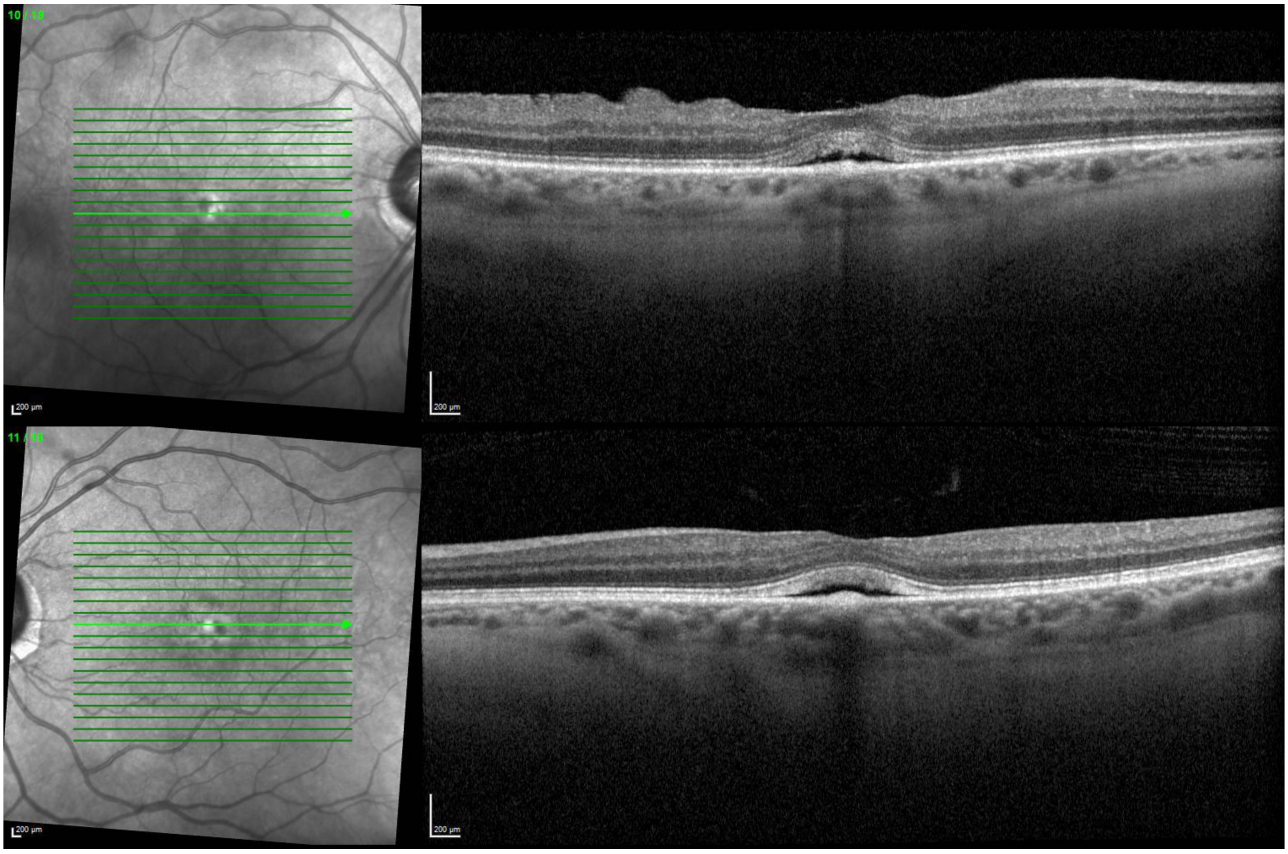

Figure 8 BRAF inhibitor associated acute exudative paraneoplastic polymorphous vitelliform maculopathy.

Vemurafenib has also been associated with a reversible acute vitelliform-like paraneoplastic maculopathy (see Figure 8).[108,109]

In addition to uveitis, MEK inhibitors can induce central serous retinopathy, subfoveal neurosensory retinal detachment, and retinal vein occlusion.[110] The most common ocular side effect of MEK inhibitors is in fact MEK inhibitor induced retinopathy. This presents as bilateral subretinal fluid accumulation with minimal visual symptoms, typically occurring within the first few weeks of treatment. Figure 9 is one example of bilateral MEK-inhibitor retinopathy with subretinal fluid. In one study of the MEK inhibitor binimetinib, retinopathy was observed in 92% of patients on MEK inhibitor monotherapy and 100% of those on BRAF/MEK inhibitor combination treatment.[111] MEK inhibitor-induced retinopathy is considered to be a class effect, and thought to be related to drug toxicity as opposed to an upregulation of the immune system as in the cases of drug-induced uveitis.[111]

Like with ICIs, the decision to discontinue the treatment depends on the severity of uveitis and the risk of drug discontinuation. Most cases of uveitis can be managed successful with local steroids and/or systemic steroid therapy. A retrospective study including 54 patients from different countries who developed uveitis while on cancer immunotherapy reported that cessation of immunotherapy was necessary only in a minority of cases. Out of all patients, 54% recovered fully or partially, 28% experienced only a single episode of uveitis, while 18% of the patients developed chronic disease.[112]

Vaccines

Another category of drug-induced uveitis is vaccine-induced uveitis. Many vaccines have been implicated in triggering ocular inflammation, including de novo uveitis or flare of existing uveitis. A recent literature review on uveitis linked to anti-viral vaccination by Zou et al[21] identified a total of 51 reported cases, involving 61 patients, spanning from 1978 to 2023. This included case reports of uveitis following vaccination against hepatitis B virus, human papilloma virus,

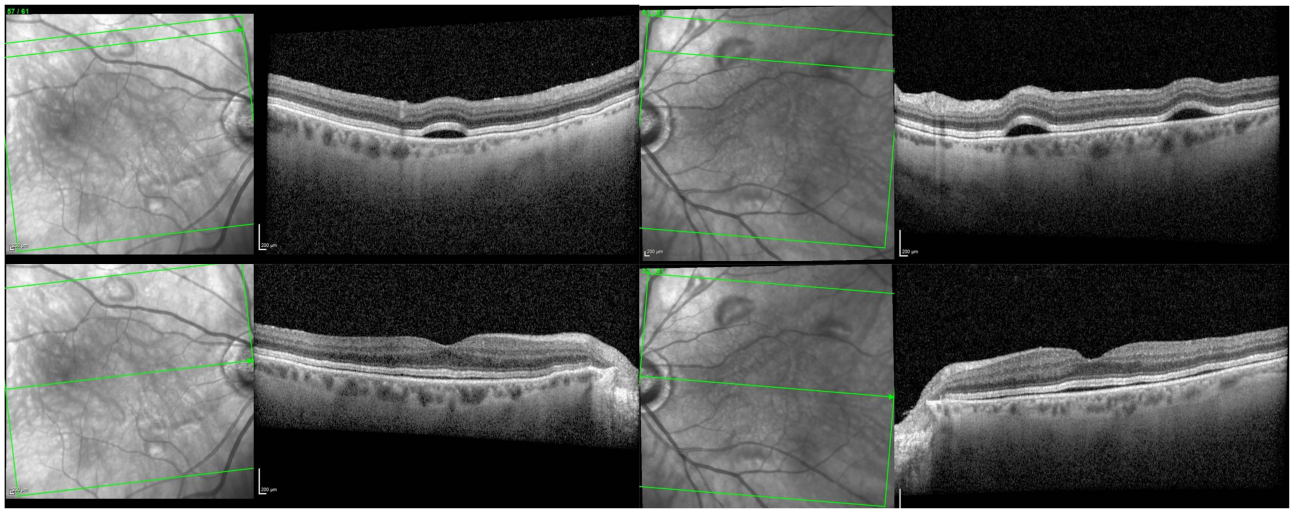

Figure 9 MEK inhibitor associated retinopathy in a patient on binimetinib for metastatic melanoma.

influenza, measles-mumps-rubella, varicella zoster virus, yellow fever, hepatitis A virus and rabies virus.[21] The time of onset reported in the majority of these cases was 24 hours to 2 weeks post vaccination. A range of uveitis types were reported, including anterior, intermediate, posterior uveitis and panuveitis, as well as distinct forms of uveitis including tubular interstitial nephritis and uveitis syndrome (TINU), VKH, acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and multiple evanescent white dot syndrome (MEWDS).[21] The authors of this present review have also treated a case of atypical APMPPE following Monkeypox (Mpox) vaccination (unpublished).

The Coronavirus disease 2019 (COVID-19) vaccines are one of the newest groups of vaccines used globally and have been the subject of scrutiny since their introduction in 2020. There is an abundance of published cases of de novo uveitis or recurrence of pre-existing uveitis after COVID-19 vaccination.[113,114] Tomkins-Netzer et al[115] conducted a population-based study of non-infectious uveitis following COVID-19 vaccination, and found an increased risk of uveitis after the first and second dose of vaccination compared to pre-vaccination. Anterior uveitis was the most common site of inflammation, occurring in 91% of eyes.[115] Types of ocular inflammation reported following COVID-19 vaccines include anterior uveitis, intermediate uveitis, posterior uveitis, panuveitis, multifocal choroiditis,[116,117] retinal vasculitis,[118,119] episcleritis and scleritis,[120] VKH disease,[121,122] MEWDS,[123,124] APMPPE,[125] acute macular neuroretinopathy (AMN),[126–128] paracentral acute middle maculopathy (PAMM)[129] and acute zonal occult outer retinopathy (AZOOR).[130–132] It has also been associated with recurrence of secondary choroidal neovascular membranes in uveitis conditions such as punctate inner choroidopathy (PIC).[133] The reported entities appear to overlap with the ocular manifestations observed in patients with COVID-19 infection, suggesting a shared immunopathogenic mechanism underlying both virus- and vaccine-mediated immune responses.[134] Jordan et al[135] published a comprehensive retrospective review of recurrence of uveitis following COVID-19 vaccination. The authors found the rate of uveitis flare was 12.3 per 1000 patient-months at baseline, 20.7 after the first dose, 15.0 after the second dose and 12.8 after the third dose. This increase in rate of uveitis recurrence was seen in both infectious and non-infectious uveitis entities. Median time to uveitis flare was 0.53 months after the first vaccination.[135]

The exact mechanism of vaccine-associated uveitis is not well-understood, but theories include molecular mimicry, antigen-specific cell and antibody-mediated hypersensitivity reactions, and reactions to vaccine adjuvants or additives.[20] Cross-reactivity occurs when peptide fragments presented to T cells closely resemble peptides of the uvea, triggering an immune response against uveal antigens. This is similar to the pathogenesis of post-infectious uveitis. Recombinant vaccines may induce delayed hypersensitivity reactions, and the deposition of immune complexes with subsequent complement activation causing uveitis.[21]

The diagnosis of vaccine-induced uveitis is based on the temporal relationship between vaccination and onset of symptoms, and the exclusion of other causes. There are no laboratory tests to confirm the diagnosis. Treatment is the

same as other drug-induced uveitis and most cases respond well to local and/or systemic steroid treatment. Most reported cases of de novo uveitis achieved complete resolution with standard treatment.[136] Although systemic steroid therapy often improves the ocular inflammation, there is a concern that immunosuppressive agents may hamper the protective immune response to vaccination.[137,138] However, real-world, population-based data provide reassuring results that vaccines remained effective in the prevention of COVID-19 in immunocompromised individuals who were taking glucocorticoids and disease-modifying antirheumatic drugs.[139]

There is also concern regarding subsequent vaccination with the same vaccine after an adverse ocular reaction. This is particularly relevant when additional doses are required to achieve optimal immunity against the targeted infection, or in the case of the influenza vaccine, annual updated doses. The COVID-19 vaccination roll-out was a vital public health tool in the management of the global pandemic, and booster doses were recommended to maximize protection against the virus. The risk of uveitis flare with subsequent boosters has not been reported, however, within the author's own series, of 48 subjects with existing uveitis who flared following COVID-19 vaccination, 29 underwent a second COVID-19 vaccine. Flares occurred in 4 subjects (13.8%), with further flares more likely if the first flare occurred ≤21 days after vaccination ($p = 0.011$).[134] Based on currently available evidence, patients with pre-existing ocular inflammatory conditions should not be discouraged from receiving COVID-19 vaccination. Additionally, there is currently insufficient evidence to support prophylactic treatment post vaccination in patients with pre-existing ocular inflammatory conditions.[113] However, patients with a background of systemic autoimmune disease or previous uveitis should be counselled regarding the potential symptoms associated with vaccine-associated uveitis.

Patients with vaccine-related uveitis should be managed on a case-by-case basis, balancing the severity of the uveitis and the benefits of vaccination. The decision to forgo future vaccinations should be made cautiously and only after thorough consultation with the patient and their primary physician.

Discussion

This review paper provides an updated overview of medications and vaccines associated with uveitis. It adds to the small number of existing review papers on the topic, since the first drug-induced uveitis review was published by Fraunfelder and Rosenbaum in 1997.[6,10,12,14,17] The most important additions in this paper are the inclusion of the novel cancer immunotherapies and the latest publications on COVID-19 vaccine related uveitis. A limitation of this review is its reliance on retrospective case series and case reports, which are inherently subject to publication and reporting bias. The incidence of uveitis caused by each drug type is therefore difficult to estimate. The diagnosis of drug-induced uveitis can be challenging in practice. The following sections provide some general guidance to aid the diagnostic process and management.

Diagnosis of Drug-Induced Uveitis

The Naranjo criteria is a standardized tool used to assess the probability that an adverse reaction is attributable to a specific medication. It comprises ten questions that either support or refute the likelihood of a drug-related event, generating a cumulative score that categorizes the reaction as "definite", "probable", "possible" or "doubtful" (Tables 1 and 2).[140] This is a useful tool when evaluating a patient with a potential drug-induced uveitis.

The diagnosis of drug-induced uveitis relies on a high index of suspicion and careful exclusion of other causes. The diagnosis should be considered if a patient presents with a new onset of ocular inflammation or a recurrence of pre-existing uveitis condition soon following initiation of a new medication. For some drugs, such as brimonidine or etanercept, the clinician should also be aware of possible late presentations. A thorough medication history, including recent ocular or systemic drug use and vaccinations, is crucial for diagnosis.

It must be emphasized that drug-induced uveitis is a diagnosis of exclusion. So standard uveitis screening investigations should still be carried out based on the patient's clinical presentation and risk factors. The investigations are necessary to rule out infectious etiologies and identify associated systemic inflammatory conditions. All new episodes of anterior uveitis should be investigated with full blood count, renal function, liver function, serum ACE, treponemal serology, HbA1c, and HLA-B27. Investigations should also include Quantiferon gold and chest X-ray for bilateral uveitis, intermediate and posterior uveitis. Urine beta-2 microglobulin and urinalysis is indicated in bilateral uveitis

Table 1 Naranjo Scale

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was readministered?	+2	−1	0	
5. Are there alternative causes that could on their own have caused the reaction?	−1	+2	0	
6. Did the reaction reappear when a placebo was given?	−1	+1	0	
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
	Total Score:			

Table 2 Naranjo Score Interpretation

Total Score	Interpretation of Scores
≥9	**Definite**. The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.
5 to 8	**Probable**. The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
1 to 4	**Possible**. The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
≤0	**Doubtful**. The reaction was likely related to factors other than a drug.

particularly if the renal function is impaired. In retinal vasculitis, further testing for systemic vasculitis should include ANCA, ANA, ENA, dsDNA, in addition to aforementioned tests for uveitis. It is important to note that drug-induced uveitis can still occur in a patient with pre-existing autoimmune uveitis, as these patients may have increased susceptibility to drug-induced inflammation, and it is not always possible to differentiate the two.

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General Advice on Management

The definitive management of a drug-induced uveitis usually requires cessation of the offending drug. However, this must be done in consultation with the patient's treating ophthalmologist and physician. As described above, anti-cancer immunotherapy can cause various ocular adverse reactions but the life-prolonging benefit of the medication may outweigh the risk of uveitis. Certain medications may have a suitable alternative that carries a lower risk of uveitis. For example, in patients with inflammatory joint disease who develop etanercept-induced uveitis, the rheumatologist may wish to switch to another TNF inhibitor such as adalimumab or infliximab. Figure 10 presents a flowchart that summarizes the diagnostic and management approach for suspected drug-induced uveitis.

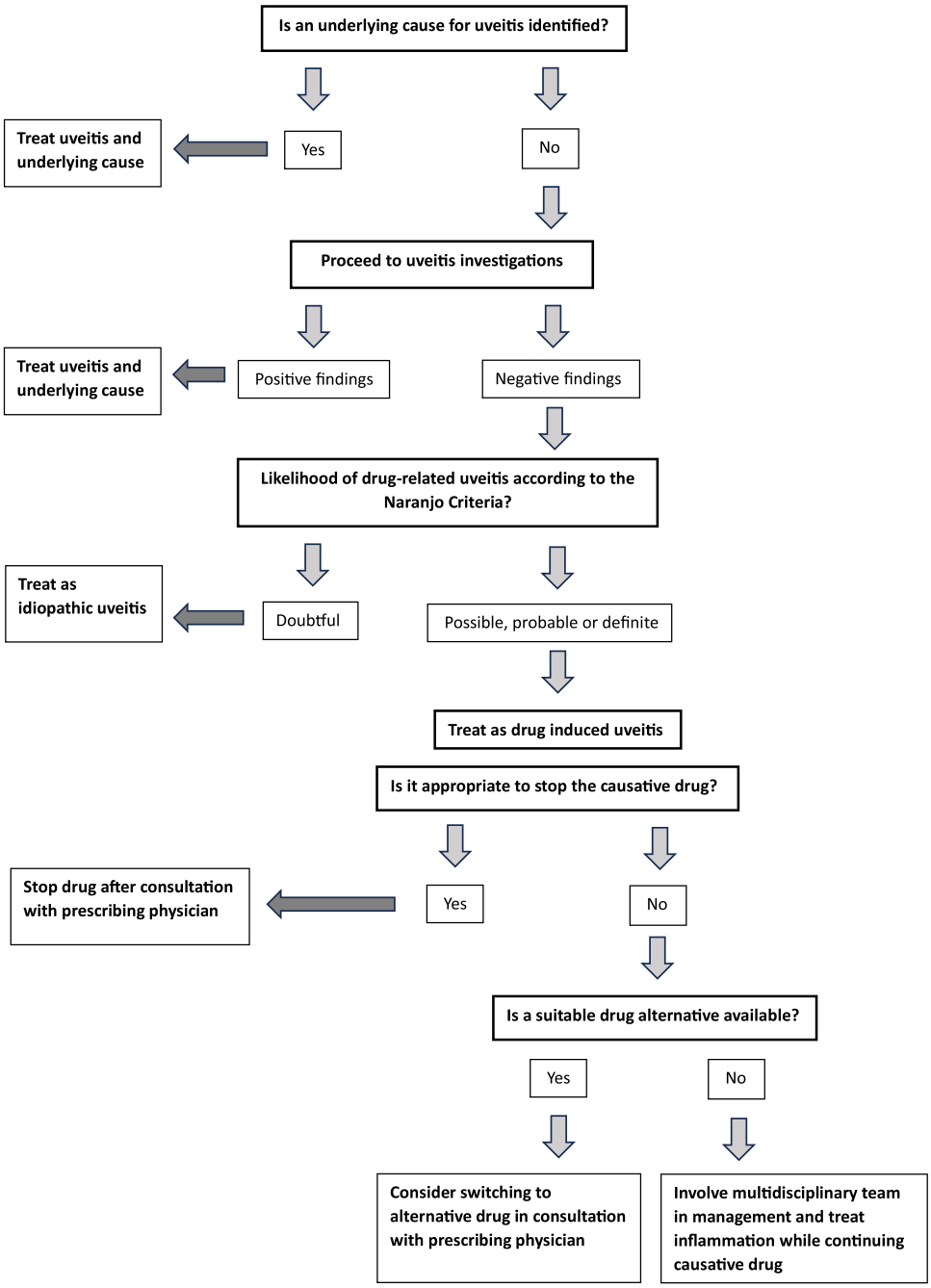

Figure 10 Diagnostic and management approach for drug-induced uveitis.

The mainstay of drug-induced uveitis treatment is corticosteroids. In anterior uveitis, topical steroids will generally suffice, while posterior uveitis and retinal vasculitis will require systemic steroid therapy or local steroid injections. Most cases of drug-induced uveitis carry a good prognosis with prompt diagnosis and treatment and recurrence is low once the causative drug is stopped. Where a rechallenge of the same medication or a trial of a different medication of the same class is planned, we recommend an ophthalmology review within 1–2 weeks of drug retrial. Working together with the patient's general practitioner and medical specialists will help prevent the future recurrence of uveitis.

Conclusion

Drug-induced uveitis is a complex and often underrecognized entity that underscores the importance of a thorough clinical assessment and a systemic drug history in patients presenting with ocular inflammation. Given the expanding range of medications implicated in uveitis, multidisciplinary collaboration between optometrists, ophthalmologists, rheumatologists, immunologists, general practitioners and pharmacologists is essential for accurate diagnosis and optimal management. Optometrists and ophthalmologists play a pivotal role in early recognition of emerging drug-related associations, as highlighted by recent cases linking vaccines to uveitis. This up-to-date and comprehensive review summarizes the current literature on drug-induced uveitis. Due to the rarity of the condition, the evidence presented consists mainly of case reports and retrospective studies, which is susceptible to reporting bias. Future prospective studies or registries to better quantify incidence and outcomes would improve our understanding of this entity. Vigilance in reporting suspected cases, coupled with robust pharmacovigilance systems, will be crucial in refining our understanding of drug-induced uveitis and mitigating its impact on patient outcomes.

Disclosure

The authors report no conflicts of interest in this work.

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