Drug-induced ocular inflammation

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ABSTRACT

AIM: Drug-induced ocular inflammation is rare and may be overlooked as a cause of uveitis. The main objective was to describe the causes of drug-induced ocular inflammation. Secondary objectives included uveitis complications and drug rechallenge reactions.

METHODS: A retrospective chart review at Auckland District Health Board's tertiary uveitis clinic (Auckland, New Zealand) was performed. Participants were identified using the uveitis database, which consists of 2,750 subjects. Fifty eyes of 35 subjects had drug-induced inflammation.

RESULTS: Drug-induced inflammation occurred in 1.3% of subjects with uveitis. Mean age was 66.8±15.6 years, and 25 subjects (71.4%) were female. Drugs responsible were bisphosphonates (24 subjects, 68.6%), brimonidine (one subject, 2.9%), etanercept (three subjects, 8.6%), immune checkpoint inhibitors (two subjects, 5.7%), BRAF inhibitors (three subjects, 8.6%), EGFR inhibitors (one subject, 2.9%) and allopurinol/perindopril (one subject, 2.9%). In subjects with bisphosphonate inflammation, anterior uveitis occurred in 22 (91.7%) and scleritis in two (8.3%). A positive rechallenge reaction occurred in two subjects with zoledronate and one with alendronate. Uveitis occurred in six subjects (17.1%) treated with cancer drugs including immune checkpoint inhibitors, BRAF inhibitors and EGFR protein kinase inhibitors. Subjects with cancer-drug-induced uveitis were managed with corticosteroids and five subjects were able to continue therapy; in one subject uveitis was uncontrollable and required drug cessation.

CONCLUSIONS: Ocular inflammation caused by bisphosphonates is usually mild and resolves on medication withdrawal. Uveitis seen in association with newer cancer medications can be more severe, but in most cases it can be managed without medication cessation.

Drug-induced ocular inflammation is relatively rare. The most common cause is bisphosphonates, but a wide number of drugs have been implicated, including, most recently, new forms of cancer drugs such as immune checkpoint inhibitors (ICPI), B-raf (BRAF) inhibitors and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors.

There are multiple mechanisms by which drugs may induce inflammation. Ocular inflammation induced by nitrogen-containing bisphosphonates is thought to be cytokine mediated[1,2], while inflammation with non-nitrogen containing bisphosphonates is idiosyncratic.[3] Cytokine mediated inflammation is also responsible for etanercept-induced uveitis.[4,5] The exact mechanism of brimonidine-induced uveitis is unknown. Possibilities for uveitis with cancer drugs include drug toxicity,[6] T cell-induced inflammation[6–9] and drug effects on subclinical uveal micrometastases.[6]

The majority of reports of drug-induced ocular inflammation are isolated case reports or small case series. The primary objective of this study was to describe the causes of drug-induced ocular inflammation. Secondary objectives included the determination of visual outcomes, complications and the outcomes of drug rechallenge.

Methods

This study received ethics approval from the Auckland District Health Board Review Committee (ethics NTX/12/EXP/085) and adhered to the tenets of the Declaration of Helsinki. The uveitis database was used to

identify subjects presenting with uveitis at Auckland District Health Board (Auckland, New Zealand) between 1 January 2008 and 1 January 2020. Subjects were excluded if they developed intraocular inflammation following intravitreal drug injection (sterile endophthalmitis).

A retrospective chart review was performed. Relevant case details were transcribed onto a standardised proforma, including demographics, inciting medication and medication indication, treatment, as well as drug discontinuation (dechallenge) and rechallenge data. Uveitic complications of band keratopathy, peripheral anterior synechiae, posterior synechiae, ocular hypertension, glaucoma, hypotony, papillitis, choroidal neovascular membrane, cystoid macula oedema (CMO) and epiretinal membrane were recorded. Ocular hypertension was defined as an intraocular pressure of ≥24mmHg. Severe vision loss (SVL) was defined, according to the Standardisation of Uveitis Nomenclature criteria, as a permanent reduction in best-corrected visual acuity (BCVA) of ≤6/60 and moderate vision loss (MVL) as a BCVA of ≤6/15.[10]

Results

The uveitis database at Auckland District Health Board (Auckland, New Zealand) consisted of 2,750 subjects. Drug-induced ocular inflammation was observed in 50 eyes of 35 subjects, representing 1.3% of subjects seen with uveitis during the study period. Subject demographics and drugs causing ocular inflammation are reported in Table 1. Mean age was 66.8±15.6 years and 25 subjects (71.4%) were female. Twenty-seven (77.1%) subjects were ≥60 years old at presentation.

The most frequent drug to cause a reaction was bisphosphonates (24 subjects, 68.6%). No subjects experienced SVL. MVL was observed in five (10%) eyes due to uncorrected refractive error (n=2, 40%), cataract (n=2, 40%) and pre-existing glaucoma (n=1, 20%).

Table 1: Subject demographics.

	N=35
Age	Mean 66.8 years ± 15.6
Female	25 (71.4%)
Ethnicity	
Caucasian	28 (80%)
Asian	5 (14.3%)
Pacific Islander	1 (2.9%)
Not stated	1 (2.9%)
Drug	
Zoledronate	22 (62.9%)
Alendronate	2 (5.7%)
Brimonidine	1 (2.9%)
Etanercept	3 (8.6%)
Erlotinib	1 (2.9%)
Vemurafenib	2 (5.7%)
Dabrafenib	1 (2.9%)
Nivolumab	1 (2.9%)
Pembrolizumab	1 (2.9%)
Allopurinol/perindopril	1 (2.9%)

Table 2: Episodes of ocular inflammation due to intravenous zoledronate and oral alendronate.

Subject	Age (years)	Gender	Laterality	Presenting visual acuity	Inflammation type	Time from drug to onset (days)	Time to resolution (days)	Positive rechallenge	Cx	Final visual acuity
Unilateral										
1	68.1	F	L	6/9	Anterior	3	20	N	OHT	6/7.5
2	65.6	F	L	6/7.5	Anterior	1	39	N	N	6/7.5
3	74.9	M	R	6/6	Anterior	6	6	N	N	6/9
4	80.2	F	L	6/18	Anterior	2	47	N	PS	6/9
5	80.1	F	L	6/9	Anterior	4	62	N	N	6/7.5
6	84.6	F	L	6/15	Anterior	5	24	N	PS	6/7.5
7	68.9	F	L	6/6	Anterior	2	63	N	N	6/6
8	77.0	F	R	6/12	Anterior	3	25	N	PS	6/9
9	81.3	F	R	6/7.5	Scleritis	5	28	N	N	6/6
10	81.0	F	R	6/9	Anterior	5	29	N	N	6/7.5
11	67.7	F	R	6/6	Anterior	2	33	N	N	6/7.5
12	71.4	F	L	6/9	Anterior	12	37	N	N	6/9
13	57.6	F	L	6/6	Anterior	4	72	Y	N	6/6
14	83.5	F	R	6/9	Anterior	20	21	Y	N	6/9
15	74.4	F	R	6/48	Anterior	7	43	N	N	6/7.5
16	76.0	F	L	NR	Scleritis	2	42	N	Cataract	6/9
17	71.8	F	L	6/12	Anterior	7	14	N	PS	6/15
18	68.3	F	L	6/7.5	Anterior	6	19	N	PS	6/9
19	63.0	F	R	6/6	Anterior	60	30	Y	N	6/9
Simultaneous bilateral										
20	60.8	F	R	6/7.5	Anterior	6	11	N	N	6/7.5
			L	6/7.5	Anterior	6	11	N	N	6/7.5
21	68.8	F	R	6/9	Anterior	7	52	N	N	6/5
			L	6/6	Anterior	7	33	N	N	6/5
22	79.4	M	R	6/60	Anterior	3	34	N	PS, cataract	6/24
			L	6/30	Anterior	3	34	N	PS	6/9
23	50.6	M	R	6/7.5	Anterior	7	22	N	N	6/6
			L	6/12	Anterior	7	22	N	N	6/6
24	75.1	F	R	6/15	Anterior	10	32	N	CMO	6/10
			L	6/10	Anterior	10	14	N		6/7.5

F=female, M=male; L=left, R=right, NR=not recorded, anterior=anterior uveitis, Cx=complication, OHT=ocular hypertension, N=no complications, PS=posterior synechiae.

Bisphosphonates

Bisphosphonate-induced inflammation occurred with zoledronate (22 subjects, 26 eyes) and alendronate (two subjects, three eyes).

Ocular inflammation following intravenous zoledronate developed 24 hours to 20 days (median: five days) after drug infusion. Eighteen (81.8%) subjects had unilateral involvement and four (18.2%) subjects had bilateral involvement. Nineteen (86.4%) subjects were female. Table 2 summarises episodes of ocular inflammation in subjects due to zoledronate . Scleritis occurred in two (9.1%) subjects: one with unilateral anterior non-necrotising scleritis, and one with unilateral anterior and posterior non-necrotising scleritis. All remaining subjects developed anterior uveitis.

Two subjects, both females, had uveitis related to oral alendronate, aged 63 and 75, shown as subject 19 and subject 24 on Table 2, respectively. Both had anterior uveitis resolving with topical corticosteroids.

Two (9.1%) patients were rechallenged with intravenous zoledronate . Both had a positive rechallenge reaction. Both subjects had complete resolution of anterior uveitis after their first episode with recurrence on re-exposure; no further episodes of uveitis occurred once the drug was ceased. In the remaining 20 (90.9%) subjects zoledronate was discontinued after their initial episode with no recurrence.

One subject with alendronate-induced uveitis discontinued the drug after their first episode with no further episodes, while the other subject continued alendronate. The subject that continued alendronate experienced a recurrent anterior uveitis 17.4 months later with no further episodes once the drug was discontinued; uveitis screen did not reveal other causes for uveitis.

All subjects with anterior uveitis were treated with topical prednisolone acetate 1% and none required systemic treatment. Inflammation resolved within 6–72 days (median: 31 days). The subject with unilateral anterior non-necrotising scleritis was treated with oral prednisone and inflammation resolved in 28 days. The subject with anterior and posterior scleritis was treated with topical corticosteroids and oral non-steroidal anti-inflammatory medications and scleritis resolved after 42 days.

All subjects recovered fully with treatment with no recurrence during the follow-up period once the drug was discontinued. Uveitic complications of posterior synechiae were observed in seven (24.1%) eyes and a secondary cataract developed in two (6.9%) eyes. One (3.4%) eye developed CMO, which resolved with topical treatment. Two eyes (6.9%) had MVL: one from cataract and one from uncorrected refractive error.

Topical brimonidine 0.2%

One subject had recurrent bilateral anterior uveitis due to topical brimonidine. This was an 82-year-old Caucasian female treated with topical brimonidine for primary open angle glaucoma. She developed bilateral anterior uveitis 57 days after commencing brimonidine, which resolved with topical prednisolone acetate 1%. Brimonidine was not discontinued after her first episode of uveitis.

She experienced recurrent bilateral anterior uveitis 7.8 months after her first episode. This second episode was managed with topical corticosteroids and resolved in 38 days. Following this second episode, brimonidine was discontinued and she had no further episodes in 5.1 years follow-up. There were no uveitic complications and uveitis screen was negative for other causes.

Tumour necrosis factor (TNF) inhibitor—subcutaneous etanercept

Etanercept-induced inflammation was observed in three subjects shown in Table 3. None of the subjects had ocular inflammation prior to commencing etanercept.

A dechallenge reaction was seen in one subject. One subject had recurrence when the drug was continued, and one had no recurrence following drug rechallenge.

A 30-year-old Asian male developed a right-sided anterior uveitis after commencing etanercept, which resolved with topical corticosteroids. Etanercept was not discontinued and a further episode of right eye anterior and intermediate uveitis occurred 2.0 years after his first episode. This second episode required topical and systemic corticosteroids, was resistant to treatment until etanercept was stopped and

Table 3: Etanercept-induced ocular inflammation.

Subject	Drug indication	Age/ Gende	Laterality	Presenting visual acuity	Ocular inflam-mation type	Time from drug to inflam-mation (days)	Treatment	Time of reso-lution (days)	Drug rechal-lenge	Cx	Final visual acuity
1	RA	66/M	R	6/7.5	Anterior uveitis	90	Topical PF	101	No	OHT	6/9
			L	6/7.5	Anterior uveitis	90	Topical PF	101	No	OHT	6/7.5
2	AS	30/M	R	6/15	Anterior uveitis	108	Topical PF	42	Yes	nil	6/6
3	AS	14/F	L	6/12	Anterior uveitis & pos-terior scleritis	390	Topical PF, periocular steroid injection, oral prednisone	45	Yes	nil	6/6

F=female, M=male, RA=rheumatoid arthritis, AS=ankylosing spondylitis, R=right, L=left, PF=prednisolone acetate 1%, Cx=complication, OHT=ocular hypertension.

took 108 days to resolve. No further episodes of uveitis occurred following drug cessation.

Drug rechallenge was observed in a 14-year-old Asian male with ankylosing spondylitis. His initial episode of anterior uveitis and posterior scleritis required topical and systemic corticosteroids and periocular steroid together with cessation of etanercept to settle. He had a drug rechallenge due to worsening joint disease 118 days after his ocular inflammation had resolved with no further recurrence.

Immune check point inhibitors (ICPI)—intravenous nivolumab and intravenous pembrolizumab

Two subjects in the uveitis database developed ICPI-related ocular inflammation.

A 50-year-old Caucasian male was receiving intravenous nivolumab infusions for metastatic renal cell carcinoma. He developed bilateral anterior and intermediate uveitis 160 days after his initial infusion with presenting visual acuities of 6/7.5 in both eyes. Uveitis was treated with topical corticosteroids resolving in 148 days. He developed left eye CMO, which resolved with topical steroid. His oncology team discontinued his nivolumab due to treatment failure and cancer progression. He had no further episodes of inflammation after stopping nivolumab during 4.9 months follow-up.

Pembrolizumab-induced bilateral uveitis was observed in a 71-year-old Caucasian man receiving infusions for mesothelioma. Bilateral anterior and intermediate uveitis developed 33 days after his initial infusion and was treated with topical and systemic corticosteroids, resolving after 17 days. His pembrolizumab was deferred, but due to tumour progression, he had a subsequent rechallenge. Initially his eyes remained quiet for 127 days, but then he developed recurrent bilateral anterior uveitis two days after his pembrolizumab dose was doubled. This second episode of uveitis was treated with topical corticosteroids and he developed secondary uveitic cataracts. He was maintained on topical corticosteroids along with pembrolizumab infusions and had no further recurrences in one-year follow-up until death from metastatic cancer.

B-raf (BRAF) inhibitors—oral vemurafenib and oral dabrafenib

Two subjects in the series had vemurafenib-induced uveitis, and another had dabrafenib-induced uveitis, summarised in Table 4.

All three subjects were receiving BRAF inhibitors for metastatic melanoma and had bilateral simultaneous uveitis. Inflammation was treated with local and systemic corticosteroids. Two subjects were able to

continue the drug but in the subject with dabrafenib-induced inflammation, uveitis was unresponsive to systemic corticosteroid therapy and required drug cessation.

All subjects developed uveitic complications. Subject 2 on Table 4 required bilateral trabeculectomies and a right glaucoma drainage device for their uveitic glaucoma.

The subject with dabrafenib-induced uveitis developed drug-induced skin toxicity with a rash and nodular tattoo reaction related to red tattoo ink. This subject had severe anterior and intermediate uveitis at initial presentation with vision reduced in count fingers in the left eye. Her dabrafenib infusions were temporarily suspended and uveitis treated with topical and systemic corticosteroids. She had a dabrafenib rechallenge with subsequent recurrent uveitis that was unable to be controlled with corticosteroid therapy and required drug cessation. There was no evidence of melanoma recurrence during follow-up once dabrafenib was discontinued.

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor—oral erlotinib

Erlotinib-related bilateral anterior uveitis occurred in a 76-year-old Caucasian man with lung adenocarcinoma. He developed simultaneous bilateral anterior uveitis 3.8 months after his initial dose and was managed with topical corticosteroid, resolving in 71 days. He was maintained on long-term topical steroid with no recurrence of inflammation following drug rechallenge. He developed uveitic cataracts and bilateral posterior synechiae. He was followed for a total duration of 3.1 years prior to death from metastatic disease with final visual acuities of 6/9 right eye and 6/15 left eye. MVL in the left eye was due to uncorrected refractive error.

Allopurinol/perindopril

A 54-year-old Asian female developed drug rash with eosinophilia and systemic symptoms (DRESS) syndrome due to either

Table 4: BRAF inhibitor induced ocular inflammation.

Subject	Drug	Age/ gender	Laterality	Presenting visual acuity	Ocular inflammation type	Time from infusion to inflammation (days)	Treatment	Time to resolution (days)	Drug discontinued	Cx	Final visual acuity
1	VM	70.2/F	R	6/9	Anterior	1,299	Topical PF	27	No	Cataract, CMO, ERM	6/9
			L	6/18	Anterior	1,326	Topical PF	31	No	CMO, ERM	6/9
2	VM	38.7/M	R	6/24	Intermediate	968	Topical PF, prednisone, orbital floor steroid injection	Ongoing	No	Cataract, PS, glaucoma, hypotony, papillitis, CNVM, CMO, ERM	6/9
			L	6/12	Intermediate	2,141	Topical PF, prednisone	Ongoing	No	Cataract, glaucoma	6/6
3	DB	54.2/F	R	6/6	Anterior & intermediate	1,377	Topical PF, prednisone	517	Yes	OHT, CMO	6/6
			L	Count fingers	Anterior & intermediate	1,377	Topical PF, prednisone	517	Yes	PS, OHT	6/6

F=female, M=male, R=right, L=left,CMO=cystoid macular oedema, ERM=epiretinal membrane, PS=posterior synechiae, CNVM=choroidal neovascular membrane, OHT=ocular hypertension, PF=prednisolone acetate 1%, VM=vemurafenib, DB=Dabrafenib, Cx=complication.

allopurinol or perindopril. She developed bilateral anterior and posterior scleritis 64 days after her initial allopurinol dose and 99 days after her initial perindopril dose. Her intraocular pressures were raised on presentation at 32mmHg right and 37mmHg left. Both drugs were discontinued.

Her scleritis was difficult to manage, requiring high-dose prednisone. Second-line immunosuppression with typical disease-modifying anti-rheumatic drugs (DMARDs) were initially contraindicated due to hepatitis secondary to DRESS. She was later started on methotrexate and active scleritis resolved after nine months.

She developed bilateral posterior subcapsular cataracts and bilateral uveitic glaucoma requiring glaucoma drainage devices. At her final follow-up, visual acuities were 6/45 right eye and 6/7.5 left eye. MVL occurred in her right eye due to cataract.

Discussion

Although presumed rare, there are few reports on the incidence of drug-induced ocular inflammation. It has been reported at less than 0.5%[11] and at our tertiary uveitis clinic comprised 1.3% of all uveitis cases. Twenty-seven subjects (77.1%) were ≥60 years, so it is an important cause of ocular inflammation in this age group.

Naranjo et al[12] proposed criteria to establish the causality of adverse events by drugs. Data contributing to causality include dechallenge, rechallenge and dose-related effects.

Bisphosphonates

Uveitis occurs in 0.29%[13] to 1.1%[14–16] and scleritis in 0.63%[13] of individuals taking bisphosphonates. Population-based studies have shown a low incidence of inflammatory eye reactions (IER) with bisphosphonates and rates of severe IER are reported to be very low.[17] In our series, only two subjects required systemic treatment and one had cystoid macular oedema, which resolved with treatment. In most, inflammation rapidly resolved with drug cessation and the use of topical corticosteroids.[2] A cycloplegic agent may be required to prevent/break posterior synechiae; seven (24.1%) eyes in this series had posterior synechiae.

Within the current study, all three subjects on bisphosphonates undergoing a drug rechallenge experienced recurrent inflammation. Most studies in the literature support recurrence of uveitis following drug rechallenge. Within small case series, positive rechallenge reactions has been documented for conjunctivitis,[18] scleritis,[19] episcleritis[18] and anterior uveitis[3,18] and again show that discontinuing bisphosphonate was required for ocular inflammation to resolve. Furthermore, uveitis recurrence was demonstrated when switching from one bisphosphonate to a different bisphosphonate agent.[20]

Conversely, Patel et al[14] did not find recurrent inflammation with repeated zoledronate infusions in three subjects with rechallenge. Additionally, Banal et al[21] found no recurrence of a unilateral anterior uveitis when zoledronate was switched to pamidronate in a single case report.

Immunologic or toxic reactions caused by the release of inflammatory cytokines are thought to be the mechanism of bisphosphonate-induced uveitis.[1,2] Uveitis can occur with non-nitrogen, halogen-containing bisphosphonates[3] and is likely an idiosyncratic reaction with these bisphosphonates,[3] therefore changing a subject onto one of these bisphosphonates may be prudent after an episode of inflammation.

Ocular hypotensive medication—brimonidine

Brimonidine is a selective alpha 2-adrenergic receptor agonist that is used for the treatment of glaucoma and ocular hypertension.

There have been a small number of case reports describing granulomatous anterior uveitis,[22–26] which tends to develop 6–9 months after initiation of medication.[2] The condition may be asynchronous, and second eye involvement can develop up to a year after the first eye.[26]

In this series, anterior uveitis recurred 7.8 months after the initial episode when brimonidine was not discontinued, but there were no further episodes following drug cessation. Other reports of dechallenge[22,26] and rechallenge[22] data make the association definite.

Tumour necrosis factor (TNF) inhibitors—etanercept

TNF is a pro-inflammatory cytokine and is the target of many immunomodulatory medications including infliximab, adalimumab and etanercept. Etanercept is a soluble TNF receptor that binds both TNF-alpha and TNF-beta and is most likely in this class to be associated with drug-induced uveitis.[2]

Ocular inflammation—which can be anterior or posterior uveitis, or scleritis—typically develops three months to two years after initiation of treatment and largely resolved after discontinuing the medication with some requiring systemic corticosteroid therapy to further settle down inflammation.[2,5,27–30]

Lim et al[27] reviewed all cases of uveitis occurring in patients treated with etanercept, infliximab and adalimumab in their national database over an eight-year period. They excluded subjects with underlying disease likely to be associated with uveitis and included those cases they felt showed causality between the drug and uveitis. The majority (43 out of 59, 72.8%) of cases were due to etanercept, 23.7% (n=14) due to infliximab and 3.4% (n=2) due to adalimumab. Etanercept was significantly more likely associated with uveitis than either infliximab (OR 5.375) or adalimumab (OR 8.60). There were also dechallenge/rechallenge data for a limited number of subjects within the etanercept group, which strengthened the association of the drug with uveitis causation.[27,28]

In our series, following cessation of etanercept in two subjects no further episodes of ocular inflammation occurred, suggesting inflammation was due to etanercept rather than the subjects' underlying autoimmune disease. In subjects developing ocular inflammation while on etanercept, alternative therapeutic options should be discussed with the subject's rheumatologist.

Cancer therapies—ICPI, BRAF inhibitors, EGFR protein kinase inhibitor

Uveitis has been documented with newer cancer immunomodulatory agents including ICPI, BRAF inhibitors and EGFR tyrosine kinase inhibitors. Six (17.1%) subjects in this study had uveitis related to cancer therapies.

ICPIs are used in the treatment of solid tumours like melanoma. Tumour cells evade host defences by activating inhibitory receptors on tumour-specific T cells; this can downregulate T-cell function allowing cancer cells to survive. ICPIs prevent activation of inhibitory receptors on tumour-specific T cells, thus enabling the T cells to become activated and kill the tumour cells.[31] Nivolumab and pembrolizumab inhibit programmed cell death protein 1 receptor, which blocks inhibitory T-cell checkpoints. ICPI-induced uveitis have been reported in all morphologies—anterior, intermediate and posterior—with anterior being most common.[31] A Vogt–Koyanagi–Harada-like syndrome has also been described including a sunset-glow fundus appearance and extraocular manifestations of hearing loss, meningismus, vitiligo and poliosis.[9,31,32]

Dysregulation of MAPK signalling and BRAF gene mutations are found in melanomas.[8] Inhibition of BRAF inhibits melanoma cell proliferation and is used in the treatment of metastatic cancer. These agents include vemurafenib and dabrafenib. Uveitis is most commonly reported with vemurafenib and fewer cases with dabrafenib.[7,33,34] Scleritis can also occur.[35] In a review of 568 subjects receiving vemurafenib, 4% developed drug-induced uveitis and were treated with ocular and systemic corticosteroid without discontinuing the drug.[6] Anterior uveitis is most common followed by intermediate uveitis.[6]

EGFR activating mutations occur in about 20% of non-small cell lung cancers and are associated with poor prognosis.[36] Erlotinib is a tyrosine kinase inhibitor and is used as a chemotherapy for non-small cell lung cancer and pancreatic cancer.[37] Anterior uveitis has been reported within six weeks of therapy[36,38] and can be treated with local steroid without stopping therapy.[39] Recurrence has been reported with lowered dosage suggesting uveitis is idiosyncratic rather than dose dependent toxicity.[36]

All these cancer therapies are potentially lifesaving. It is important to weigh the risks and benefits of these agents. If it is potentially lifesaving, it should not be discontinued; the drug reaction should be

treated locally instead.[36,39,40] There have been few cases of severe ocular inflammation requiring drug cessation.[41,42] Fortunately, the majority of drug-induced uveitis improve with topical, regional or systemic corticosteroid therapy without needing to discontinue therapy. The risk of biologic and non-biologic DMARDs in the treatment of uveitis in these patients is unknown. Those that continued therapy experienced relapses of uveitis unless maintained on corticosteroid.[31]

In this series nivolumab was discontinued without recurrence. Pembrolizumab-induced uveitis recurred following rechallenge and continued local steroid therapy prevented further recurrences while continuing the drug. Vemurafenib-induced intermediate uveitis was also treated with continued local steroid therapy to prevent recurrent uveitis. In all cases complications of chronic uveitis including cataract, CMO, glaucoma and posterior synechiae occurred. One subject developed significant uveitic glaucoma requiring glaucoma surgery. Severe anterior and intermediate uveitis related to dabrafenib occurred in one subject reducing vision to count fingers in one eye at presentation; the drug was temporarily suspended then rechallenged with recurrent uncontrollable uveitis that required drug cessation. Withdrawal, discontinuation and rechallenge data exists for verurafenib[40] and erlotinib[36], strengthening the association between these drugs and uveitis.

Allopurinol/perindopril

Both allopurinol[43] and perindopril[33] can induce DRESS syndrome. However, ocular inflammation from allopurinol- and perindopril-induced DRESS syndrome has not been described previously. Furthermore, this is the first case of scleritis as an ocular manifestation of DRESS syndrome.

DRESS syndrome is a delayed type IVb hypersensitivity reaction with a mortality of up to 10%.[45] It is a severe, idiosyncratic multisystem reaction to a drug and commonly occurs within eight weeks after starting the offending drug. Treatment involves early recognition, prompt cessation of all suspected drugs and supportive local and systemic treatment including corticosteroids.[46]

Cicatrising conjunctivitis is the most common ocular manifestation of DRESS syndrome; intraocular inflammation is rare. Cases of uveitis (anterior, intermediate, panuveitis,)[46,47] and two cases of uveal effusion syndrome[48,49] have been reported in the literature. This is the first case of scleritis as a symptom of DRESS syndrome.

Conclusion

Drug-induced ocular inflammation is an uncommon but important cause of uveitis. Management begins with consideration of a drug-related event and requires clinician awareness. Anterior uveitis is the most common clinical picture, visual acuity tends to be minimally affected and, if the drug is ceased, uveitis does not recur. Severe cases, while rare, can cause future management concerns; our series demonstrates that recurrent uveitis can occur with repeat administration of the medication. An approach with pre-treatment of topical steroid before an infusion may have merit, but it requires study to see if this reduces risk of recurrence.

Immunomodulatory cancer drugs require special consideration. Inflammation can range from minimal to severe, requiring local and sometimes systemic corticosteroid treatment. The risk of persistent ocular inflammation needs to be balanced with potential cancer progression if the drug is discontinued. Chronic mild inflammation can be managed with long-term topical therapy to prevent recurrence while maintaining a lifesaving drug. In cases of severe vision threatening inflammation, the drug may, however, need to be discontinued. In all such cases, careful communication and joint care with the treating oncologist is recommended.

Competing interests:
Nil.

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