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Ocular adverse events associated with antibody-drug conjugates used in cancer: Focus on pathophysiology and management strategies

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ABSTRACT

Antibody-drug conjugates (ADCs) are designed to maximize cancer cell death with lower cytotoxicity toward noncancerous cells and are an increasingly valuable option for targeted cancer therapies. However, anticancer treatment with ADCs may be associated with ocular adverse events (AEs) such as dry eye, conjunctivitis, photophobia, blurred vision, and corneal abnormalities. While the pathophysiology of ADC-related ocular AEs has not been fully elucidated, most ocular AEs are attributed to off-target effects. Product labelling for approved ADCs includes drug-specific guidance for dose modification and management of ocular AEs; however, limited data are available regarding effective strategies to minimize and mitigate ocular AEs. Overall, the majority of ocular AEs are reversible through dose modification or supportive care. Eye care providers play key roles in monitoring patients receiving ADC therapy for ocular signs and symptoms to allow for the early detection of ADC-related ocular AEs and to ensure the timely administration of appropriate treatment. Therefore, awareness is needed to help ophthalmologists to identify treatment-related ocular AEs and provide effective management in collaboration with oncologists as part of the patient's cancer care team. This review provides an overview of ocular AEs that may occur with approved and investigational ADC anticancer treatments, including potential underlying mechanisms for ADC-related ocular AEs. It also discusses clinical management practices relevant to ophthalmologists for prevention, monitoring, and management of ADC-related ocular AEs. In collaboration with

Abbreviations: AcBut, 4-(4′-acetylphenoxy)-butanoic acid; ADC, antibody-drug conjugate; ADL, activities of daily living; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AXL, receptor tyrosine kinase AXL; BC, breast cancer; BCMA, B-cell maturation antigen; BCVA, best-corrected visual acuity; BRAF, proto-oncogene B-Raf; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; DMH, 2-dimethyl hydrazine dichloride; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire; FxRn, Fc region receptor; FGFR, fibroblast growth factor receptor; FR, folate receptor; GA, gastric adenocarcinoma; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor 3; HR, hormone receptor; HRQoL, health-related quality of life; Ig, immunoglobulin; LSCD, limbal stem cell deficiency; LY6E, lymphocyte antigen 6 complex locus E; mAb, monoclonal antibody; mBC, metastatic breast cancer; MCC, 4-(N-maleimidomethyl) cyclohexane- 1-carboxylate; mc-val-cit-PABC, maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl; MEC, microcystic-like epithelial change; MEK, mitogen-activated protein kinase; MF, mycosis fungoides; MM, multiple myeloma; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; NaPi2b, sodium-dependent phosphate transport protein 2B; NEI-VFQ-25, National Eye Institute Visual Function Questionnaire 25; NHL, non-Hodgkin lymphoma; NR, not reported; NSCLC, non-small cell lung cancer; OSDI, Ocular Surface Disease Index; PABC, p-aminobenzyloxycarbonyl; PBD, pyrrolobenzodiazepine; pcALCL, primary cutaneous anaplastic large cell lymphoma; PTCL, peripheral T-cell lymphoma; PTK7, protein tyrosine kinase 7; q2w, every 2 weeks; q3w, every 3 weeks; q4w, every 4 weeks; qw, every week; RFcγ, receptors for the Fc region of IgG; RRMM, relapsed or refractory multiple myeloma; sALCL, systemic anaplastic large cell lymphoma; SPDB, N-succinimidyl 4-(2-pyridyldithio)butyrate; TF, tissue factor; TfR1, transferrin receptor 1; TKIs, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell-surface antigen 2; VC, valine citrulline.

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oncologists, ophthalmologists play a vital role in caring for patients with cancer by assisting with the prompt recognition, mitigation, and management of treatment-related ocular AEs.

1. Introduction

Antibody-drug conjugates (ADCs) are targeted cancer therapies that consist a cytotoxic drug linked, via a chemical linker, to a monoclonal antibody (mAb) that targets a protein selectively expressed on cancer cells (Marks and Naidoo, 2022). Due to this conjugation, ADCs are designed to maximize cancer cell death while minimizing the toxicity to noncancerous cells (Marks and Naidoo, 2022).

Multiple anticancer treatments, from conventional to the most recent ones like ADCs

And other targeted agents, are known to be associated with ocular adverse events (AEs). Ocular AEs caused by established cytotoxic anticancer treatments, such as cytarabine and docetaxel, are well recognized, and their severity ranges from asymptomatic to vision-threatening (Liu et al., 2023). Newer targeted agents have also been associated with ocular AEs, including immune checkpoint inhibitors and signal transduction inhibitors (e.g., mitogen-activated protein kinase [MEK] inhibitors, tyrosine kinase inhibitors [TKIs], fibroblast growth factor receptor [FGFR] inhibitors, proto-oncogene B-Raf [BRAF] inhibitors, epidermal growth factor receptor [EGFR] inhibitors, and ADCs) (Bindiganavile et al., 2021; Davis, 2016; Fortes et al., 2021; Liu et al., 2023; Stjepanovic et al., 2016; Vishnevskia-Dai et al., 2021). Ocular surface AEs, including dry eye, conjunctivitis, photophobia, blurred vision, and corneal abnormalities (e.g., microcyst-like epithelial changes, keratitis, and keratopathy), are the most frequently reported and well-recognized eye-related AEs with ADC treatment (Eaton et al., 2015; Fortes et al., 2021). These ocular symptoms can negatively impact health-related quality of life (HRQoL) and cause interruption or

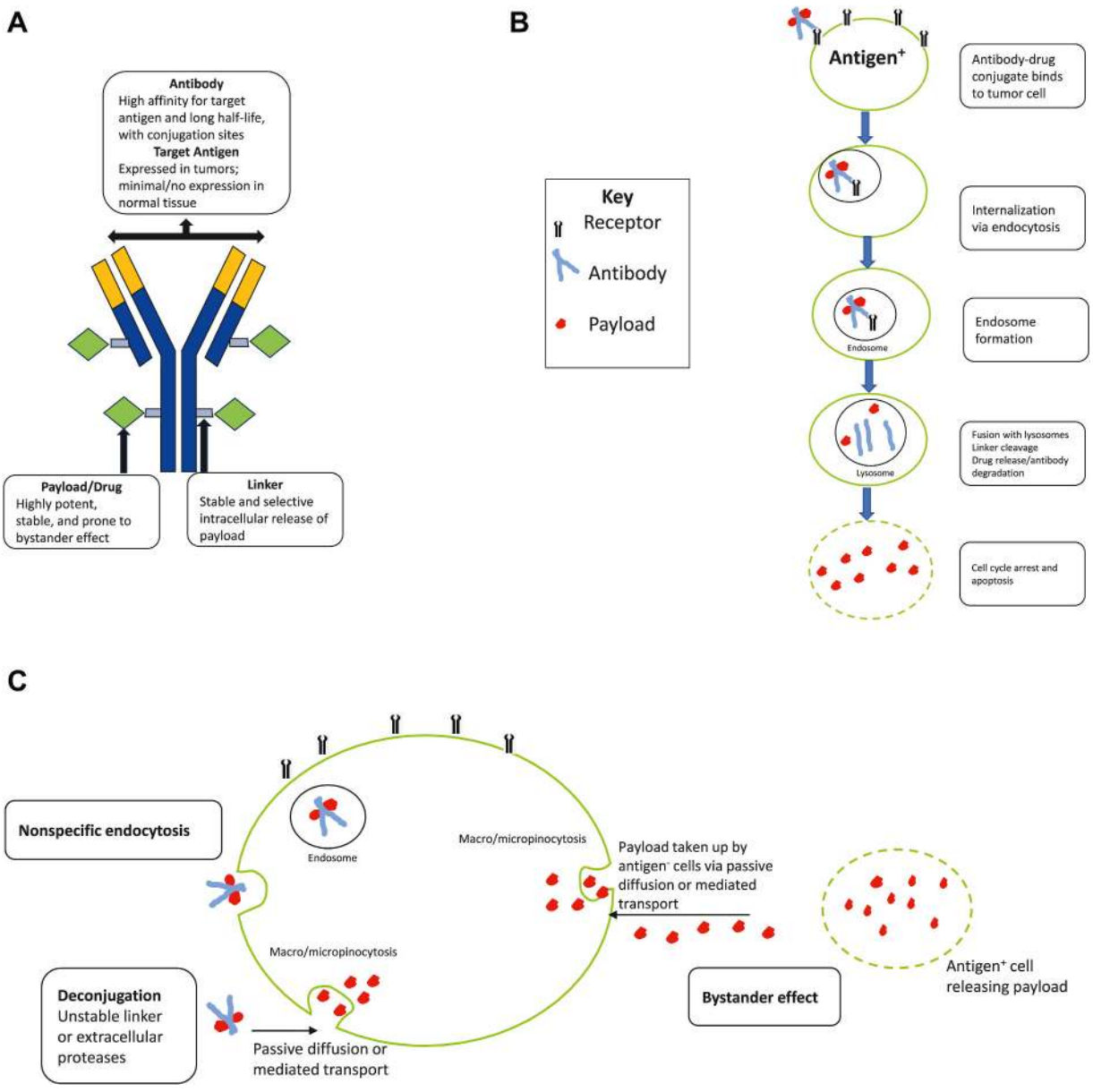

Fig. 1. (A) Structure of antibody-drug conjugates (ADCs); (B) basic mechanism by which ADCs exert anticancer activity; (C) potential mechanisms for ADC or free payload uptake in normal cells. ADC, antibody-drug conjugate.

discontinuation of anticancer therapy (Davis, 2016; Fortes et al., 2021; Liu et al., 2023), potentially affecting clinical outcomes in patients with cancer.

This narrative review provides an overview of the ocular AEs that may occur during anticancer treatment with ADCs and describes aspects of their clinical management that are relevant to practicing clinical ophthalmologists. It also summarizes the current knowledge of ocular AEs with approved/developmental ADCs, including theoretical, pharmacological, and practical aspects on the current status of ADCs as a treatment modality in oncology. A specific focus on the types, frequency, and severity of ocular AEs associated with ADCs is proposed. The purpose of this article is to raise awareness among ophthalmologists to help them identify and anticipate ocular AEs in their patients and to provide information from current guidelines and expert opinions. This article also includes recommendations for future research.

1.1. Overview of ADCs

ADCs are an increasingly important class of therapies for treating solid and hematological cancers. The three components of an ADC, the mAb, cytotoxic drug (also known as the 'payload' or 'warhead'), and linker (Fig. 1A), are all critical to treatment success, affecting the ADC's safety, potency, and efficacy (Donaghy, 2016; Marks and Naidoo, 2022; Trail, 2013).

For an optimized ratio between efficacy and safety, the mAb needs to bind specifically and effectively to its target antigen on cancer cells while avoiding normal non-cancer cells to minimize the risk of AEs (Donaghy, 2016). Most mAbs used in ADCs are immunoglobulin (Ig) G1 or IgG4 antibodies that are designed to target tumor-specific sites (Trail, 2013). Conjugated to the mAb is the cytotoxic payload, which exerts its effects on critical cellular processes required for survival.

Once the mAb binds to its target receptor on the cancer cell surface, the receptor–ADC complex is internalized via endocytosis. Subsequently, the linker is biochemically cleaved or spontaneously degrades to release the cytotoxic payload at sufficient concentrations to act on its intracellular target (Fig. 1B) (Marks and Naidoo, 2022; Trail, 2013). Payloads are often cytotoxic in the picomolar concentration range, which is crucial, because only a very small amount (<1%) of the antibody dose is localized to the tumor (Donaghy, 2016). This is due to limited penetration of the antibody into the tumor and/or poor linker stability, resulting in the remaining antibody dose being systemically released (Beck et al., 2017; Kondrashov et al., 2023).

Classes of payloads include microtubule inhibitors; topoisomerase inhibitors, which inhibit deoxyribonucleic acid (DNA) replication thereby inducing apoptosis; as well as calicheamicin derivatives, pyrrolobenzodiazepine dimers, and alkylating agents, all of which damage cellular DNA (Binaschi et al., 1995; Damia and D'Incalci, 1998; Donaghy, 2016; Marks and Naidoo, 2022; Trail, 2013). A summary of the currently approved and investigational ADCs is provided in Table 1.

2. Proposed pathophysiology of ADC-related ocular AEs

Increased risk of ocular AEs with the use of ADCs may be related to the cytotoxic payload, as ocular AEs are more common with ADCs that contain the microtubule inhibitors DM4 (a derivative of maytansine) or monomethyl auristatin F (MMAF) (Donaghy, 2016; Eaton et al., 2015) (see Table 2). However, the fact that not all microtubule inhibitors have similar toxicity suggests that the mode of action of the payload may not fully explain the observed differences between MMAF and other inhibitors like MMAE or DM1. For MMAF-conjugated ADCs, toxicity may be related to intracellular accumulation (Donaghy, 2016). In contrast, ocular AEs are not very commonly described for ADCs that utilize the microtubule inhibitors monomethyl auristatin E (MMAE) or DM1 (a derivative of maytansine) (Donaghy, 2016; Eaton et al., 2015). This disparity indicates that factors such as the quality of the link with the ADC or other variables may also play a significant role.

Although the exact mechanism underlying ADC-related ocular AEs is not completely understood, several factors make the cornea especially vulnerable to AEs, such as the abundance and variety of cell surface receptors, and rapidly growing cell subpopulations (Domínguez-Llamas et al., 2023). Further, ocular tissues allow for direct, detailed histological-like examination through methods like slit-lamp examination, which is not possible in other organs. Additionally, the terminal nature of limbal vessels and the high metabolic activity of the corneal epithelium may render it more susceptible to potential toxicity. Corneal sensitivity and retinal discrimination power is further compounded by its dense network of nerves, which can quickly trigger noticeable symptoms even with slight abnormalities (Dua and Said, 2019; Yang et al., 2018b). Overall, the pathophysiology of ocular AEs following ADC treatment can be categorized into on-target and off-target toxicity, with off-target toxicity believed to be the major mechanism of ADC-related ocular AEs (Domínguez-Llamas et al., 2023; Mahalingaiah et al., 2019).

Most ADC-related ocular AEs are corneal in nature (Eaton et al., 2015), corneal toxicity is regularly found for ADCs targeting various epitopes not expressed on the corneal surface (Mahalingaiah et al., 2019). The reason for the corneal distribution of these ADCs has been the subject of hypotheses, including the bathing of the corneal epithelial cells by tears, which are a transudate of blood (Farooq et al., 2020), and the simple passive diffusion from the peri-corneal terminal vasculature (Mahalingaiah et al., 2019). A reduction in blood flow to this terminal vascularization has been shown by both physical means (application of cold) and pharmacological means (vasoconstrictors applied to the ocular surface throughout the treatment or simply during the period surrounding the infusions) to decrease the diffusion of GFP labelled antibody into the corneal stroma (Roopenian and Akilesh, 2007).

The corneal limbus region is particularly important in explaining the pathophysiology of ADCs' AEs, due to the presence of both epithelial and stromal corneal cell progenitors, immune cells, and a high nerve density. Because the IgG Fc receptor and the neonatal Fc receptor are expressed on corneal cell surface, they play a crucial role in increasing the stability, resistance to degradation and extending the half-life of antibodies, including ADCs within these cells (Giragossian et al., 2013; Martins et al., 2016; Niu et al., 2011). This prolonged presence and recycling of ADCs in corneal cells may lead to the accumulation of these complexes (Brachet et al., 2016; Powner et al., 2014; Roopenian and Akilesh, 2007; Wang et al., 1989).

The long half-life of ADCs due to their recycling by the neonatal Fc region receptor (FcRn) increases exposure to healthy tissues, and the receptors for the Fc region of IgG (RFcγ) expressed on many cells of the immune system can bind these ADCs, both of which could amplify off-target toxicity in the cornea (Brachet et al., 2016; Powner et al., 2014; Wang et al., 1989).

Macropinocytosis, the nonspecific, actin-dependent internalization of large amounts of extracellular fluid, solutes, and membrane in large endocytic vesicles, is another mechanism that potentiates ADCs entry into corneal cells, contributing to their off-target toxicity (Zhao et al., 2017, 2018). This process is discussed in further detail below. Modulation of macropinocytosis through pharmacological modulation of the cellular process or by decreasing positive charges present on ADCs (Zhao et al., 2018) has shown promising results in experimental settings.

2.1. On-target toxicity

As the name suggests, on-target toxicity involves the target-dependent uptake of ADCs. This type of toxicity can occur when the target antigen is not only expressed on cancer cells, but also on normal corneal cells. For example, HER2, a receptor expressed by corneal cells, is targeted by HER2-directed drugs such as trastuzumab emtansine and trastuzumab duocarmazine (Mahalingaiah et al., 2019). Similarly, the membrane-spanning mucin MUC16, which is highly expressed on corneal cells, is targeted by MUC16-directed drugs, including the discontinued investigational ADCs sofituzumab vedotin (DMUC5754A)

Table 1
Currently approved or investigational antibody-drug conjugates (ADCs).

ADC (manufacturer)	mAb (target)	Payload (type)	Linker type	Indication(s) [phase(s) of development]	Ocular toxicity reported
Approved ADCs					
Belantamab mafodotin (GSK)[a]	IgG1 (BCMA)	MMAF (auristatin microtubule inhibitor)	Maleimidocaproyl	RRMM [approved]	Yes (European Medicines Agency, 2022b; Farooq et al., 2020; GlaxoSmithKline, 2022)
Brentuximab vedotin (Seattle Genetics, Inc.)	IgG1 (CD30)	MMAE (maytansinoid microtubule inhibitor)	Dipeptide (VC)	Classical Hodgkin lymphoma; other CD30-expressing PTCL; sALCL; pcALCL; MF; Pediatric patients ≥2 years with Classical Hodgkin lymphoma [all approved]	No (Seagen Inc., 2023a; Vaklavas and Forero-Torres, 2012)
Enfortumab vedotin (Astellas Pharma US, Inc.)	IgG1 (Nectin-4)	MMAE (auristatin microtubule inhibitor)	mc-val-cit-PABC	Urothelial cancer [approved]	Yes (Agensys, Inc and Seagen Inc, 2023; European Medicines Agency, 2022d)
Gemtuzumab ozogamicin (Pfizer Inc.)	IgG4 (CD33)	N-acetyl ɣ-calicheamicin 1,2 DMH	Condensation product of AcBut and Dimethylhydrazide	AML [approved]	No (Ali et al., 2019; Wyeth Pharmaceuticals LLC, 2021; Xu et al., 2021)
Inotuzumab ozogamicin (Pfizer Inc.)	IgG4 (CD22)	N-acetyl ɣ-calicheamicin	Condensation product of AcBut and Dimethylhydrazide	ALL [approved]	No (European Medicines Agency, 2022a; Wyeth Pharmaceuticals LLC, 2018)
Loncastuximab tesirine (ADC Therapeutics SA)	IgG1 (CD19)	SG3199 (PBD dimer)	Valine-alanine	Large B-cell lymphoma [approved] B-cell ALL, B-cell NHL [Phase 1–2]	No (ADC Therapeutics SA, 2022; European Medicines Agency, 2023b)
Mirvetuximab soravtansine (ImmunoGen, Inc.)	IgG1 (FR alfa)	Ravtansine (maytansinoid microtubule inhibitor)	Sulfo-SPDB	Epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer [all approved]	Yes (ImmunoGen, Inc., 2022)
Polatuzumab vedotin-piiq (Genentech, Inc.)	IgG1 (CD79b)	MMAE (maytansinoid microtubule inhibitor)	mc-val-cit-PABC	Large B-cell lymphoma [approved]	No (European Medicines Agency, 2022e; GenentechInc., 2023)
Sacituzumab govitecan (Immunomedics)	IgG1 (Trop-2)	SN-38 (topoisomerase I inhibitor)	CL2A (PABC-containing)	TNBC [approved] HR-positive, HER-2 negative BC [approved] Urothelial cancer [accelerated approval]	No (European Medicines Agency, 2022f; Gilead SciencesInc., 2023)
Tisotumab vedotin (Seagen, Inc.)	IgG1 (TF)	MMAE (auristatin microtubule inhibitor)	mc-val-cit-PABC	Cervical cancer [approved]	Yes (2023b)
Trastuzumab deruxtecan (Daiichi SankyoInc., 2022)	IgG1 (HER2)	Deruxtecan (topoisomerase I inhibitor)	Maleimide tetrapeptide	HER2+ BC [approved] HER2-low BC [approved] HER2-mutant NSCLC [approved] HER2+ GA or GEJA [approved]	Yes (Daiichi SankyoInc., 2022; European Medicines Agency, 2023a)
Trastuzumab emtansine (Genentech, Inc.)	IgG1 (HER2)	Mertansine (maytansinoid microtubule inhibitor)	MCC	HER2+ BC [approved]	Yes (European Medicines Agency, 2022c; GenentechInc., 2022)
Investigational ADCs					
Anetumab ravtansine (Bayer AG)	IgG1 (mesothelin)	Ravtansine (maytansinoid microtubule inhibitor)	SPDB	Pleural mesothelioma [Phase 2] Ovarian cancer and pancreatic adenocarcinoma [both Phase 1]	Yes (Kindler et al., 2022; Santin et al., 2023; Spiliopoulou et al., 2022)
ARX788 (Novocodex Biopharmaceuticals Co. Ltd.)	IgG1 (HER2)	AS269 (tubulin inhibitor)	Para-acetyl-phenylalanine	HER2+ metastatic BC [Phase 1]	Yes (Zhang et al., 2022)
Cofetuzumab pelidotin (AbbVie)	IgG1 (PTK7)	Auristatin-0101 (microtubule inhibitor)	Dipeptide (VC)	Solid tumors [Phase 1]	No (Maitland et al., 2021)
Coltuximab ravtansine (ImmunoGen, Inc.)	IgG1 (CD19)	Ravtansine (maytansinoid microtubule inhibitor)	SPDB	Diffuse large B-cell lymphoma, ALL [all Phase 2]	Yes (Coiffier et al., 2016; Kantarjian et al., 2016; Trněný et al., 2018)
CX-2029 (CytomX Therapeutics)	NR (TfR1)	MMAE (auristatin microtubule inhibitor)	Dipeptide (VC)	Solid tumors [Phase 1]	No (Johnson et al., 2021)
Datopotamab deruxtecan (Daiichi Sankyo Co., Ltd)	IgG1 (Trop-2)	Exatecan derivative (topoisomerase I inhibitor)	Tetrapeptide	Solid tumors (NSCLC, HER2– BC) [Phase 1–3]	Yes (Krop et al., 2022)
DLYE5953A (Genentech, Inc.)	IgG1 (LY6E)	MMAE (auristatin microtubule inhibitor)	mc-val-cit-PABC	Solid tumors [Phase 1]	Yes (Tolaney et al., 2020)
ELU001 (Elucida Oncology)	IgG1 (FR alfa)	Exatecan derivative (topoisomerase I inhibitor)	Cathepsin-B	Solid tumors [Phase 1–2]	No data (NCT05001282) (Ma et al., 2022)
Indatuximab ravtansine (Biotest Pharmaceuticals Corp.)	IgG4 (CD138)	Ravtansine (maytansinoid microtubule inhibitor)	SPDB	MM [Phase 1–2]	No (Jagannath et al., 2019; Kelly et al., 2021)
Mecbotamab vedotin (BioAtla, Inc.)	IgG1 (AXL)	MMAE (auristatin microtubule inhibitor)	mc-val-cit-PABC	Solid tumors [Phase 1–2] NSCLC, ovarian cancer, soft tissue sarcoma [all Phase 2]	No data (NCT04681131; NCT03425279)
Patritumab deruxtecan (Daiichi Sankyo, Inc.)	IgG1 (HER3)	Exatecan derivative (topoisomerase I inhibitor)	Tetrapeptide	NCSLC [Phase 1]	No (Jänne et al., 2022)

(*continued on next page*)

Table 1 (*continued*)

ADC (manufacturer)	mAb (target)	Payload (type)	Linker type	Indication(s) [phase(s) of development]	Ocular toxicity reported
Praluzatamab ravtansine (CytomX Therapeutics, Inc.)	IgG1 (CD166)	Ravtansine (maytansinoid microtubule inhibitor)	SPDB	HR+/HER2– BC [Phase 2]	Yes (Boni et al., 2022)
Telisotuzumab vedotin (AbbVie, Inc.)	IgG1 (c-Met)	MMAE (maytansinoid microtubule inhibitor)	Dipeptide (VC)	NSCLC [Phase 3]	No (Camidge et al., 2021)
Trastuzumab duocarmazine (Byondis B.V.)	IgG1 (HER2)	*Seco*-duocarmycin-hydroxybenzamide-azaindole (alkylating agent)	Dipeptide (VC)	HER2+ BC [Phase 3]	Yes (Banerji et al., 2019; Saura Manich et al., 2021)
Tusamitamab ravtansine (Sanofi)	IgG1 (CEACAM5)	Ravtansine (maytansinoid microtubule inhibitor)	SPDB	Solid tumors [Phase 1] NCSLC [Phase 3] BC, pancreatic cancer, gastric cancer [all Phase 2]	Yes (Gazzah et al., 2022)
Upifitamab-rilsodotin (Mersana Therapeutics)	IgG1 (NaPi2b)	Auristatin F-hydroxypropylamide (auristatin microtubule inhibitor)	Thioether	Ovarian cancer [Phase 3] NSCLC [Phase 2]	No data (NCT03319628; NCT04907968; NCT05329545)

AcBut, 4-(4′-acetylphenoxy)-butanoic acid; ADC, antibody-drug conjugate; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AXL, receptor tyrosine kinase; BC, breast cancer; BCMA, B-cell maturation antigen; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; DMH, 2-dimethyl hydrazine dichloride; FR, folate receptor; GA, gastric adenocarcinoma; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor 3; HR, hormone receptor; Ig, immunoglobulin; LY6E, lymphocyte antigen 6 complex locus E; mAb, monoclonal antibody; mc-val-cit-PABC, maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl; MCC, 4-(N-maleimidomethyl) cyclohexane- 1-carboxylate; MF, mycosis fungoides; MM, multiple myeloma; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; NaPi2b, sodium-dependent phosphate transport protein 2B; NHL, non-Hodgkin lymphoma; NR, not reported; NSCLC, non-small cell lung cancer; PABC, p-aminobenzyloxycarbonyl; pcALCL, primary cutaneous anaplastic large cell lymphoma; PBD, pyrrolobenzodiazepine; PTCL, peripheral T-cell lymphoma; PTK7, protein tyrosine kinase 7; RRMM, relapsed or refractory multiple myeloma; sALCL, systemic anaplastic large cell lymphoma; SPDB, N-succinimidyl 4-(2-pyridyldithio)butyrate; TF, tissue factor; TfR1, transferrin receptor 1; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell-surface antigen 2; VC, valine citrulline.

[a] No longer marketed in the United States.

and DMUC4064A (Blalock et al., 2007; Liu et al., 2021). In addition, tisotumab vedotin is a tissue factor-directed ADC; tissue factor is expressed in human ocular surface cells, specifically the conjunctiva (Ando et al., 2011). Overall, however, on-target toxicity is not believed to be a common cause of ADC-related ocular AEs, as ADCs are developed to target sites that are not present or have limited presence in the body in normal conditions (Mahalingaiah et al., 2019).

2.2. Off-target toxicity

Unlike on-target toxicity, off-target toxicity is target independent (Domínguez-Llamas et al., 2023; Mahalingaiah et al., 2019). The majority of ADC-related ocular AEs are thought to occur because of off-target toxicity, with multiple mechanisms and factors contributing to this type of pathophysiology (Mahalingaiah et al., 2019). These factors and mechanisms include suboptimal linker stability, receptor-mediated endocytosis, nonspecific endocytosis, and bystander effect (Fig. 1C) (Domínguez-Llamas et al., 2023; Mahalingaiah et al., 2019).

2.2.1. Effect of linker stability and conjugation

Stability of the ADC linker is an important consideration in the design of ADCs, as it has important safety and efficacy implications. That is, an unstable linker can result in the premature release of the cytotoxic payload, before it reaches its target, potentially resulting in cytotoxicity in unintended regions via passive diffusion or transporter-mediated uptake (Fig. 1C) (Domínguez-Llamas et al., 2023; Mahalingaiah et al., 2019). This is particularly significant in ocular surface conditions where protease activity, including matrix metalloproteinases or cathepsins, is increased.

To minimize off-target toxicity, the linker that conjugates the cytotoxic payload to the mAb is a major subject of research in an attempt to increase its stability and selectivity to proteases (Donaghy, 2016; Trail, 2013). The variability in toxicity may be attributed to the efficacy and stability of linkers. In general, linkers are classified by their mechanism of cytotoxic payload release: cleavable linkers are mainly cleaved in endosomes or lysosomes via acidic degradation (e.g., hydrazones), proteolytic degradation by cathepsin B (e.g., those with dipeptide bonds, such as valine-citrulline), or thiol-disulfide exchange reactions (e.g., those with disulfide or carbonate bonds), whereas non-cleavable linkers (e.g., maleimidocaproyl and succinimidyl 4-[N-maleimidomethyl] cyclohexane-1-carboxylate) require complete lysosomal proteolytic degradation of the mAb (Donaghy, 2016). Original ADCs had acid-cleavable linkers vulnerable to serum protease cleavage; more recent ADCs, however, are designed with non-cleavable linkers, which appear to improve linker instability issues contributing to off-target toxicity (Mahalingaiah et al., 2019).

Furthermore, conventional ADCs use nonspecific conjugation methods (with surface exposed amino acids) that produce heterogeneous ADCs vulnerable to decreased plasma stability, which results in loss of the cytotoxic payload in the plasma and ultimately increases toxicity. Suboptimal linker stability can result in premature drug release, especially in ocular surface conditions where protease activity, including matrix metalloproteinases or cathepsins, is increased. The presence or history of ocular surface inflammation (OSI) should be investigated before ADC treatment, as it may explain ocular side effects unrelated to the ADC dose. Recent engineering efforts have focused on improving conjugation methods by using specific amino acids to generate more homogenous ADCs that are less prone to off-target toxicity (Mahalingaiah et al., 2019). These technologies include cysteine-based conjugation approaches, such as chemically defined cysteine-engineered antibody-tubulysin conjugates (Thompson et al., 2016) and a cysteine-engineered antibody conjugated to pyrrolobenzodiazepine using a self-immolative disulfide linker, to yield highly stable ADCs with improved safety versus conventional ADCs (Pillow et al., 2017).

2.2.2. Receptor-mediated endocytosis

Off-target ocular AEs may also result from target-independent receptor-mediated uptake of ADCs (Mahalingaiah et al., 2019). Receptors, including FcγRs, FcRn, and C-type lectin receptors, recognize and bind the highly conserved Fc regions of IgG antibodies on ADCs, potentially resulting in ADC internalization into normal cells (Fig. 1C) (Mahalingaiah et al., 2019). This internalization can be linked to the terminal nature of limbal vasculature, which facilitates the centripetal

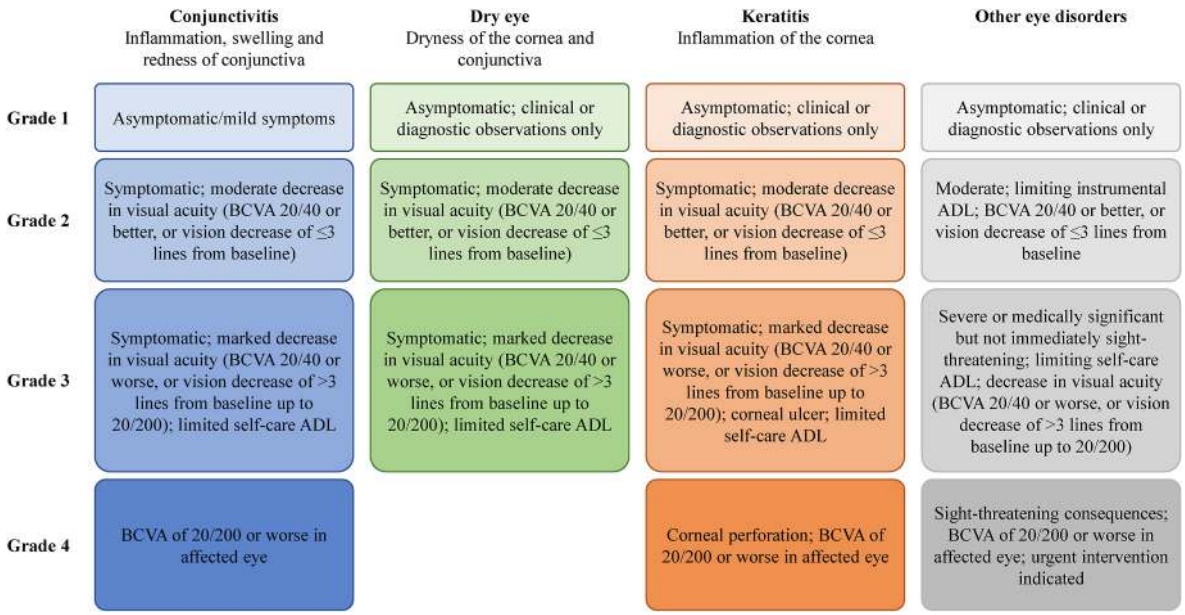

Fig. 2. Definitions of key ocular adverse events associated with antibody-drug conjugates according to Common Terminology Criteria for Adverse Events (National Cancer Institute, 2017). ADL, activities of daily living; BCVA, best-corrected visual acuity.

diffusion of antibodies into the cornea. This phenomenon is implicated in the pathophysiology of corneal immunologic disorders, such as Wessely rings, Mooren ulcers, and Pseudo-Mooren ulcers. The interaction of ADCs with immunoglobulin receptors on epithelial cell surfaces may lead to local accumulation, theoretically potentiating off-target corneal side effects.

2.2.3. *Nonspecific endocytosis*

Nonspecific endocytosis, including macropinocytosis and micropinocytosis (nonspecific internalization of very small vesicles containing extracellular fluid, solutes, and membrane), is the most likely explanation for ocular AEs, particularly macropinocytosis, due to ADC uptake by normal corneal epithelial cells (Fig. 1C) (Mahalingaiah et al., 2019). Macropinocytosis involves the development of ruffled extensions of the plasma membrane in areas of abundance of extracellular fluid to facilitate endocytosis (Mahalingaiah et al., 2019). This mechanism occurs in various cell types, some of which include B and T cells, fibroblasts, epithelial cells, and endothelial cells, but it is especially prominent in cancer cells, dendritic cells, and macrophages, where micropinocytosis is a constitutive process (Lin et al., 2020). The cornea is rich in macrophages and dendritic cells (Frutos-Rincón et al., 2022), which may make it especially vulnerable to off-target toxicity via micropinocytosis.

2.2.4. *Bystander effect*

Off-target toxicity can result from a bystander effect, a phenomenon that occurs when, after reaching its target, free payload released from antigen-positive target cells travels to the extracellular space due to cell permeability of a cell, high lipophilicity of the payloads, or diminished cell integrity following cell death—and then enters the intracellular space of antigen-negative normal cells via passive diffusion, transporter-mediated uptake, or nonspecific endocytosis to cause damage of the non-cancerous surrounding cells (Fig. 1C) (Mahalingaiah et al., 2019). The bystander effect of ADCs, where therapeutic agents affect not only targeted cells but also adjacent healthy cells as “collateral” damage, may exacerbate inflammation on the ocular surface, contributing to increased ADC-related side effects.

3. Ocular AEs with ADCs

Descriptions of the key ocular AEs according to Common Terminology Criteria for Adverse Events (CTCAE) grade are provided in Fig. 2.

3.1. *Corneal AEs*

3.1.1. *The different clinical patterns of ADC-associated keratopathy*

Several reports have described ocular AEs with ADCs in clinical trials. Of note, the level of detail provided for these AEs has varied considerably across individual reports. Many targeted anticancer agents, including ADCs, have ocular toxicities, as reviewed by Fortes et al. (2021). The most common ADC-related ocular AEs are corneal in nature and include distinct clinical phenotypes that remain to be precisely delineated. Based on the literature and our clinical experience, we observed 3 distinct clinical phenotypes: i) superficial microcystic-like epithelial changes (MECs) of the cornea (MEC keratopathy), ii) superficial punctate keratitis and keratoconjunctivitis, and iii) limbal stem cell deficiency (LSCD).

MECs are bilateral lesions of the corneal epithelium that typically present early after treatment initiation as translucent epithelial inclusions in the corneal periphery on slit lamp examination, with a whorl-like pattern with fluorescein staining under cobalt blue light (Deklerck et al., 2019; Farooq et al., 2020; Rousseau et al., 2020). Although these intraepithelial lesions start in the corneal periphery, they may migrate towards the central cornea and promote epithelial thickening (Farooq et al., 2020; Rousseau et al., 2020). A retrospective case series study of 29 patients with ADC-related keratopathy demonstrated that MECs were significantly associated with hyperopic shifts (peripheral MECs) and myopic shifts (paracentral/central MECs), which corresponded to corneal steepening and resulted in reductions in visual acuity (Bui et al., 2022; Canestraro et al., 2022; Rousseau et al., 2020). A recent retrospective study confirmed that vision fluctuations are a major sign of MECs migrating to the center of the cornea and requiring particular attention (Chauver J et al. Use of refractive shift in patients treated by belantamab mafodotin for follow up. Manuscript submitted). An example of microcystic MEC keratopathy with hyperopic shift patterns is shown in Fig. 3 (unpublished data).

Keratitis and keratoconjunctivitis present as red, watery eyes that are

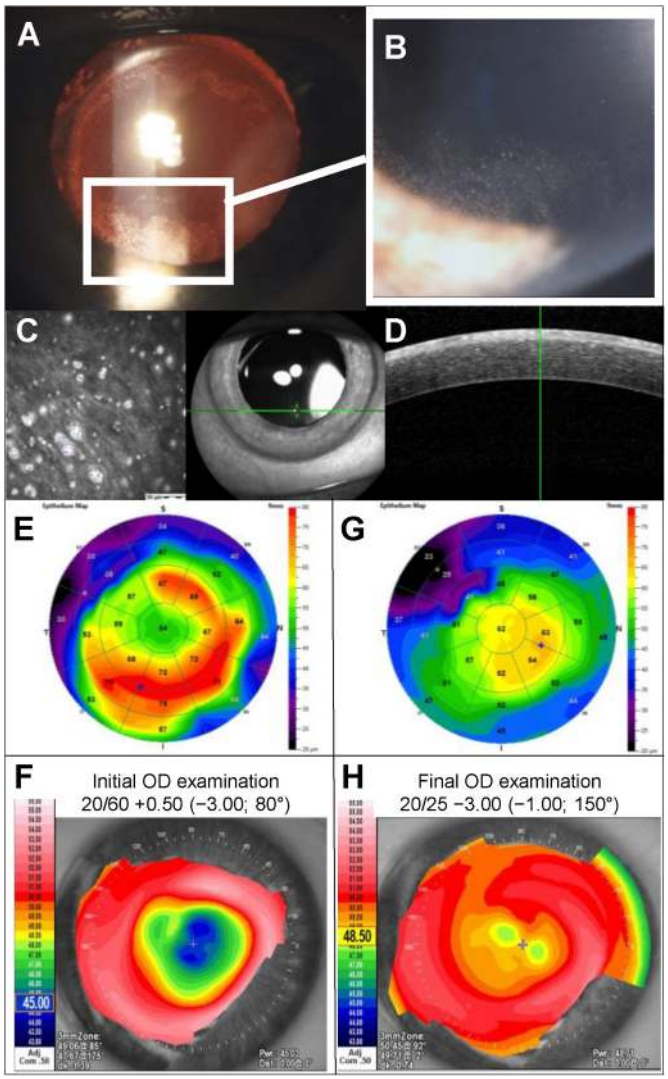

Fig. 3. Belantamab mafodotin-induced microcystic like epithelial keratopathy. A woman in her sixties presented with a +3 diopters hyperopic shift in both eyes 1 week after a second infusion of belantamab mafodotin for refractory multiple myeloma. (A, B) Bilateral microcystic opacities were observed in the peripheral corneal epithelium, with (C) hyperreflective intracellular dots seen by in vivo confocal microscopy, (D, E) a hyperreflective and thickened aspect observed by optical coherence tomography, and (F) an oblate, postmyopic surgery topography. After discussion with the hematologist, the next infusion was postponed by 3 weeks. (G) Opacities migrated into the central cornea and vanished, while (H) vision recovered and refraction, epithelial mapping, and topography normalized. Reproduced with permission from Rousseau A, Michot JM, Labetoulle M. Belantamab mafotodin-induced epithelial keratopathy masquerading myopic surgery. *Ophthalmology*. 2020 Dec; 127 (12):1626.

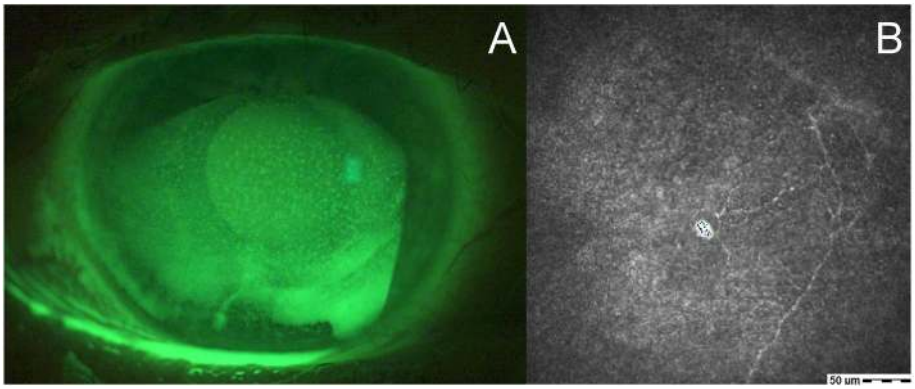

Fig. 4. Superficial punctate keratopathy induced by tisotumab vedotin (anti tissue factor). (A) Superficial punctate keratopathy in a female patient in her fifties who received tisotumab vedotin (antitissue factor) for 5 months. (B) In vivo confocal microscopy scan showing rarefaction of corneal nerves at the epithelial subbasal plexus level.

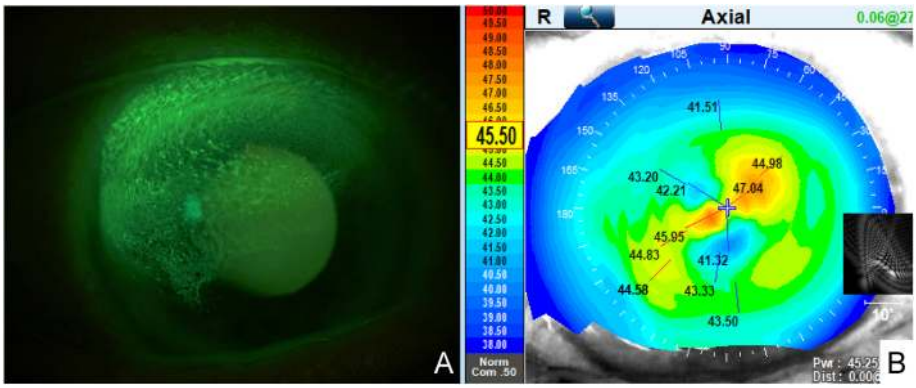

Fig. 5. Hurricane keratopathy indicative of limbal stem cell deficiency in a female patient in her sixties undergoing treatment with datopotamab deruxtecan (anti-TROP2) for a lung adenocarcinoma (Visual acuity = 20/100). (A) Slit lamp photograph post-fluorescein instillation. (B) Corneal topography revealing irregular astigmatism.

sensitive to light with potentially impaired vision and are caused by underlying ocular surface inflammation. A case of keratoconjunctivitis combining pseudomembranous conjunctivitis, meibomitis, and subsequent diffuse superficial punctate keratitis associated with tisotumab vedotin has been reported (Parikh et al., 2024). An example of superficial punctate keratitis in a female patient in her fifties who received the tissue factor-directed tisotumab vedotin for 5 months, and who had decreased corneal sensitivity and underlying corneal denervation (see following) is shown in Fig. 4 (unpublished data).

LSCD has not yet been reported in the literature (to our knowledge) as a consequence of ADC treatment. However, we managed two cases of ADC-associated hurricane keratopathy, indicative of LSCD. This type of keratopathy is characterized by a whorl pattern and occurs secondary to a previous disappearance (e.g., traumatic) of corneal epithelial cells that can be transitory or more persistent in the case of LSCD. In one unpublished case study, a female patient in her sixties, following treatment with the TROP2-directed datopotamab deruxtecan for lung adenocarcinoma, developed hurricane keratopathy (Fig. 5). Pre-treatment data was unavailable; however, the patient reported the onset of ocular surface disease (OSD) symptoms during treatment. Datopotamab deruxtecan was discontinued due to ocular toxicity and lack of efficacy. This discontinuation, combined with the use of bandage contact lenses, steroids, and lubricants, resulted in significant clinical improvement. Nevertheless, after six months of follow-up, mild hurricane keratopathy persists with limited repercussions. The second case involved a male patient in his forties with refractory oropharyngeal epidermoid carcinoma, who developed hurricane keratopathy following treatment with tisotumab vedotin. Pre-treatment data was also unavailable in this case, but the symptoms started during treatment. He presented with severe keratoconjunctivitis combined with hurricane keratopathy. Treatment was interrupted, showing mild improvement but was swiftly replaced by an anti-EGFR monoclonal antibody that may have impaired epithelial healing. The patient received topical steroids and lubricants with limited efficacy and is scheduled to receive autologous serum eyedrops.

3.1.2. Corneal nerve toxicity

Additionally, case series studies have documented corneal nerve toxicity, severe reduction of subbasal corneal nerve fiber density (Fig. 4), and reduced corneal sensitivity with certain ADCs, such as belantamab mafodotin and the investigational drug depatuxizumab mafodotin (Aschauer et al., 2022; Parrozzani et al., 2020). It is important to note here that belantamab mafodotin was initially FDA approved for relapsed or refractory multiple myeloma (RRMM) under accelerated approval but was removed from the US market following failure to meet requirements of the confirmatory Phase 3 trial. Loss of corneal nerves induces corneal hypoesthesia and thus reduced lacrimal reflex, together with reduced epithelium turnover and repair (Aschauer et al., 2022). Both aspects pave the way for the development of dry eye disease, and eventually, if the process persists, to neurotrophic keratopathy, with potentially severe persistent epithelial defect or even corneal perforation (Shaheen et al., 2014; Yang et al., 2018a).

The pathophysiology underlying corneal nerve toxicity following belantamab mafodotin treatment, which has an MMAF payload, may be explained by the nonspecific uptake of the ADC in the nerves, resulting in disruption of microtubules and ultimately neurodegeneration. This is supported by in vitro studies that showed that MMAF binds broadly to microtubules, inhibiting proliferation and mitosis and causing widespread microtubule damage (Best et al., 2021).

3.2. Noncorneal AEs

Albeit less frequent than corneal AEs, noncorneal AEs have been reported with ADC use. As mentioned previously, pseudo membranous conjunctivitis and meibomitis with a good clinical response to topical steroids have been reported in a patient treated by tisotumab vedotin (Parikh et al., 2024). In addition, cataracts have also been noted with ADC use. For example, cataract was among the Grade 3 eye disorder events, as defined using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) criteria, that were reported in two patients in a study of 28 patients receiving trastuzumab emtansine for advanced HER2+ breast cancer (Beeram et al., 2012).

4. Mitigation and management of ADC-related ocular AEs

Most of the ocular AEs seen with ADCs are mild and reversible (i.e., Grade 1–2) and can be managed with dose modifications or delayed infusion and supportive care (Eaton et al., 2015). However, involvement of eye care professionals, including ophthalmologists, optometrists, or other eye care specialists (Kim et al., 2022) may be necessary in certain cases, such as when ocular AEs develop and do not resolve or worsen (Seagen Inc., 2023a,b; European Medicines Agency, 2022d). Some ocular AEs may necessitate the reduction, discontinuation or even interruption of anticancer treatment (after a close collaboration between the ophthalmologist and the patient's oncologist), but most others may be managed with topical ocular treatments without discontinuation of cancer treatment (Fortes et al., 2021).

Consideration also should be given to the involvement of any other targeted therapies that are used in combination with the ADC, given their association with ocular AEs. Although there are no consensus guidelines for the mitigation and management of ADC-related ocular AEs, recommendations have been made, either in product labelling information (European Medicines Agency, 2022b, d; ImmunoGenInc.,

Table 2
Reported ocular adverse events with currently approved or investigational antibody-drug conjugates (ADCs).

ADC	Indication (population size)	ADC dosage	Ocular toxicities
Approved ADCs			
Belantamab mafodotin[a]	RRMM (n = 95) (Lonial et al., 2020)	2.5 mg/kg q3w	**Corneal AEs** Keratopathy[b]: 71% (all grades), 27% (Grade 3) Blurred vision[c]: 22% (all grades); 4% (Grade 3) Dry eye[d]: 14% (all grades), 1% (Grade 3)
Enfortumab vedotin	Advanced urothelial carcinoma (n = 296) (Powles et al., 2021)	1.25 mg/kg on days 1, 8, and 15 of 28-day cycle	**Corneal AEs** Corneal disorders: 1% (all grades) Dry eye: 16% (all grades), 1% (Grade 3) Blurred vision: 4% (all grades)
Mirvetuximab soravtansine	Platinum-resistant ovarian cancer (n = 106) (Matulonis et al., 2022)	6 mg/kg q3w	**Corneal AEs** Keratopathy: 36% (all grades), 9% (Grade ≥3) Blurred vision: 41% (all grades), 6% (Grade ≥3)
Tisotumab vedotin	Recurrent or metastatic cervical cancer (n = 102) (Coleman et al., 2021)	2.0 mg/kg q3w	**Corneal AEs** Keratitis: 11% (Grade 1–2) Ulcerative keratitis: 2% (Grade 3) Dry eye: 23% (Grade 1–2) **Noncorneal AEs** Conjunctivitis: 26% (Grade 1–2)
Trastuzumab deruxtecan	HER2+ BC (n = 184) (Modi et al., 2020)	5.4 mg/kg q3w	**Corneal AEs** Dry eye: 12% (all grades)
Trastuzumab emtansine	HER2+ mBC (n = 884) (GenentechInc., 2022)	3.6 mg/kg q3w	**Noncorneal AEs** Blurred vision: 5% (all grades) Dry eye: 4% (all grades)
			Noncorneal AEs Conjunctivitis: 4% (all grades) Lacrimation increased: 3% (all grades)
	HER + Advanced mBC (n = 28) (Beeram et al., 2012)	escalating weekly doses, starting at 1.2 mg/kg	Eye disorders: 14% (all grades) **Corneal and noncorneal AEs** Cataract, ocular surface disease, and punctuate keratitis: 2 patients (Grade 3)
	Early HER2+ BC (n = 740) (Genentech, Inc., 2022)	3.6 mg/kg q3w	**Corneal AEs** Blurred vision: 4% (all grades) Conjunctivitis: 4% (all grades)
Investigational ADCs			
Anetumab ravtansine	Pleural mesothelioma (n = 163) (Kindler et al., 2022)	6.5 mg/kg q3w	**Corneal AEs** Corneal disorder: 40% (all grades), 2% (Grade 3) Dry eye: 13% (all grades)
	Platinum-resistant ovarian cancer (n = 9) (Santin et al., 2023)	5.5 or 6.5 mg/kg q3w + pegylated liposomal doxorubicin	**Corneal AEs** Corneal epithelial changes: 48% (Grade 1–2) Corneal disorder: 29% (all grades) Dry eye: 17% (all grades) Blurred vision: 14% (all grades), 3% (Grade 3)
	Advanced pancreatic adenocarcinoma (n = 33) (Spiliopoulou et al., 2022)	5.5 or 6.5 mg/kg q3w + nivolumab, nivolumab-ipilimumab, or nivolumab-gemcitabine	**Corneal AEs** Keratitis: 3% (Grade 2) Blurred vision: 15% (Grade 1–2) **Noncorneal AEs** Xerophthalmia: 3% (Grade 1)
ARX788	HER2+ mBC (n = 69) (Zhang et al., 2022)	1.5 mg/kg q3w or 0.88–1.3 mg/kg q4w	**Corneal AEs** Corneal epitheliopathy: 46% (all grades), 4% (Grade ≥3) Blurred vision: 22% (all grades), 3% (Grade ≥3) **Noncorneal AEs** Xerophthalmia: 22% (all grades) Eye disorders: 19% (all grades)
Coltuximab ravtansine	Diffuse large B-cell lymphoma (n = 52) (Coiffier et al., 2016)	55 mg/m^2 qw for 4 weeks, then q2w for 8 weeks + rituximab	**Corneal AEs** Corneal events: 6% (all grades) **Noncorneal AEs** Extracorneal events: 12% (all grades) Lacrimal events: 8% (all grades)
	Diffuse large B-cell lymphoma (n = 61) (Trněný et al., 2018)	55 mg/m^2 qw for 4 weeks, 1 week rest, then q2w	Eye disorders: 25% (Grade 1–2) **Corneal AEs** Keratitis: 2% (Grade 2) Dry eye: 3% **Noncorneal AEs** Extracorneal eye disorders: 21%
	ALL (n = 36) (Kantarjian et al., 2016)	55–90 mg/m^2 q2w	Ocular adverse events: 25% (Grade 1–2) **Corneal AEs** Keratitis: 3% Blurred vision: 14% **Noncorneal AEs** Extracorneal events: 17% Lacrimal disorder: 6%
Datopotamab deruxtecan	TNBC (n = 43) (Krop et al., 2022)	6 mg/kg q3w	**Noncorneal and corneal AEs**

(*continued on next page*)

Table 2 (*continued*)

ADC	Indication (population size)	ADC dosage	Ocular toxicities
			Dry eye, retinal exudates, blurred vision requiring dose reduction (incidences not reported)
DLYE5953A	Refractory solid tumors (n = 68) (Tolaney et al., 2020)	0.2–2.4 mg/kg q3w	**Corneal AEs** Dry eye: 13% **Noncorneal AEs** Lacrimation increased: 10%
Praluzatamab ravtansine	Advanced solid tumors (n = 99) (Boni et al., 2022)	0.25–10 mg/kg q3w or 4–6 mg/kg q2w	**Corneal AEs** Keratitis: 21% (all grades), 9% (Grade ≥3) Keratopathy: 3% Corneal infiltrates: 1% Blurred vision: 16% Dry eye: 8% **Noncorneal AEs** Photophobia: 3% Orbital cyst: 1%
Trastuzumab duocarmazine	Metastatic solid tumors and HER2+ BC (n = 146) (Banerji et al., 2019)	1.2 mg/kg q3w	**Corneal AEs** Keratitis: 17% (Grade 1–2), 2% (Grade 3) Dry eye: 30% (Grade 1–2), 1% (Grade 3) Blurred vision: 10% (Grade 1–2), 1% (Grade 3) **Noncorneal AEs** Conjunctivitis: 28% (Grade 1–2), 3% (Grade 3) Lacrimation increased: 20% (Grade 1–2) Retinal hemorrhage: 1% (Grade 3) Bacterial conjunctivitis: 1% (Grade 3)
Tusamitamab ravtansine	Advanced solid tumors (n = 31) (Gazzah et al., 2022)	5–150 mg/m^2 q2w	**Corneal AEs** Keratopathy: 26% (Grade 1–3); 19% (Grade 3) Keratitis: 3% (Grade 1–2) Punctate keratitis: 3% (Grade 3) Dry eye: 13% (Grade 1–2) Blurred vision: 13% (Grade 1–2)
	Non-squamous CEACAM5+ NSCLC treated for ≥12 months (n = 11) (Ricordel et al., 2022)	100 mg/m^2 q2w	**Corneal AEs** Keratitis/keratopathy: 73% (all grades), 36% (Grade ≥3)

ADC, antibody-drug conjugate; ALL, acute lymphoblastic leukemia; BC, breast cancer; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; qw, every week; q2w, every 2 weeks; q3w, every 3 weeks; q4w, every 4 weeks; RRMM, relapsed or refractory multiple myeloma; TNBC, triple-negative breast cancer.

[a] No longer marketed in the United States.

[b] Defined as corneal epithelium changes (±symptoms) on ophthalmic examination.

[c] Included blurred vision, diplopia, reduced visual acuity, and visual impairment.

[d] Included dry eye, ocular discomfort, eye pruritus, and foreign-body sensation in the eye.

2022; Seagen Inc., 2023a,b) or by study investigators (Gazzah et al., 2022; Kim et al., 2022; Lonial et al., 2021), for several individual ADCs that are known to be associated with ocular AEs (Table 3). It is important to note here that mitigation and management recommendations vary based on the clinical evidence of the individual ADC and should not be generalized across ADCs.

4.1. Prevention of ocular AEs

Several prophylactic measures that generally mitigate ADC-related ocular AEs have been proposed (European Medicines Agency, 2022b, d; Gazzah et al., 2022).

4.1.1. Topical lubricant

Regular use of prophylactic lubricating eye drops (e.g., preservative-free artificial tears) before and during treatment with belantamab mafodotin or enfortumab vedotin is recommended, as well as avoidance of contact lenses (Agensys, Inc and Seagen Inc, 2023; European Medicines Agency, 2022b, d; GlaxoSmithKline, 2022).

4.1.2. Corticosteroid

Data from Phase 1 and 2 clinical studies have shown contradictory results with regard to the effectiveness of prophylactic ophthalmic corticosteroid eye drops in preventing corneal epithelial changes with tusamitamab ravtansine, belantamab mafodotin, tisotumab vedotin or mirvetuximab soravtansine (de Bono et al., 2019; Gazzah et al., 2022; Lonial et al., 2020; Matulonis et al., 2019). Prophylactic measures, including the use of topical corticosteroid eye drops for the first 3 days of treatment, reduced the incidence of conjunctivitis in the Phase 1–2 InnovaTV 201 study of tisotumab vedotin in patients with advanced or metastatic solid tumors (de Bono et al., 2019). The use of corticosteroid eye drops as prophylaxis for conjunctival disorders is recommended as part of the eye care plan for patients receiving tisotumab vedotin, with administration prior to and for 72 h after infusion (Kim et al., 2022). Similarly, primary prophylaxis with corticosteroid eye drops showed a trend towards a lower incidence of keratopathy compared with no prophylaxis in a Phase 1 trial of mirvetuximab soravtansine in patients with relapsed ovarian cancer (Matulonis et al., 2019). Although mirvetuximab soravtansine is not yet approved in Europe, the US prescribing information for this ADC recommends prophylaxis with ophthalmic topical corticosteroids (ImmunoGen, Inc., 2022). In contrast, the application of primary prophylaxis (including with an ocular corticosteroid gel) during treatment with tusamitamab ravtansine did not alleviate ocular toxicity in a Phase 1 dose-escalation study in patients with advanced solid tumors, and the maximum tolerated dose was determined to be 100 mg/m^2 (Gazzah et al., 2022). Prophylactic corticosteroid eye drops were also ineffective in preventing keratopathy in the Phase 2 DREAMM-2 study of belantamab mafodotin in patients with RRMM, with a similar incidence of Grade 3 keratopathy in treated versus untreated eyes, and a similar median time to keratopathy between eyes (Lonial et al., 2020). This inconsistency between studies clearly suggests that ocular AEs of ADCs likely differ according to the target of the MAb, the nature of the linker and the mode of action of the payload.

Table 3
Recommended strategies for minimizing and mitigating ocular adverse events for specific antibody-drug conjugates (ADCs).

ADC	Recommendations for mitigating and managing ocular toxicities		
	Prophylactic measures	During treatment	Should ocular toxicity occur
Belantamab mafodotin[a] (European Medicines Agency, 2022b; GlaxoSmithKline, 2022; Lonial et al., 2021)	• Ocular examination (visual acuity and slit lamp) prior to initiation • Administer preservative-free artificial tears ≥4 times daily from the first day of infusion and during treatment • Avoid contact lenses unless directed by an ophthalmologist	• Regular ocular examinations (visual acuity and slit lamp)	• Ocular examination (visual acuity and slit lamp) promptly for worsening symptoms and <2 weeks prior to and ≥1 week after each dose • For moderate or severe AEs, withhold treatment until improvement, then resume at same or reduced dose (1.9 mg/kg) • For worsening symptoms that are unresponsive to management, consider permanent discontinuation
Enfortumab vedotin (Agensys, Inc. and Seagen Inc., 2023; European Medicines Agency, 2022d)	• Administer artificial tears to mitigate dry eye	• Regular ocular examinations • Advise patients to contact their healthcare provider if they experience any visual changes	• Ocular examination • Consider ophthalmic topical steroids if indicated after an ocular examination • Consider dose interruption or dose reduction for symptomatic ocular disorders
Mirvetuximab soravtansine (ImmunoGen, Inc., 2022)	• Ocular examination (visual acuity and slit lamp) by an eye care professional prior to initiation • Administer artificial tears/lubricant eye drops before and during treatment • Administer ophthalmic topical steroids before and during treatment • Avoid contact lenses unless directed by a healthcare provider	• Regular ocular examinations (visual acuity and slit lamp) by an eye care professional • Advise patients to contact their healthcare provider if they experience any visual changes	• Ocular examination (visual acuity and slit lamp) by an eye care professional promptly for new or worsening signs and symptoms • Withhold treatment until improvement and resume at same or reduced dose; dosage modifications/ discontinuation depend on the type, persistence, and severity of the ocular AE • Discontinue for Grade 4 ocular toxicities
Tisotumab vedotin (Kim et al., 2022; Seagen Inc., 2023b)	• Ocular examination (visual acuity and slit lamp) prior to initiation • Administer lubricant eye drops and ophthalmic topical steroids before and during treatment • Administer vasoconstrictor eye drops immediately before each infusion • Utilize cold packs • Avoid contact lenses unless directed by an eye care provider	• Regular ocular examinations (visual acuity and slit lamp) by an eye care professional • Advise patients to contact their healthcare provider if they experience any visual changes	• Ocular examination (visual acuity and slit lamp) by an eye care professional promptly for new or worsening signs and symptoms • Withhold or reduce dose, or permanently discontinue treatment based on the type, persistence, and severity of the ocular AE

ADC, antibody-drug conjugate; AE, adverse event.
[a] No longer marketed in the United States.

4.1.3. *Reducing blood flow (cold + vasoconstrictors)*

The US prescribing information for tisotumab vedotin recommends the use of topical ocular vasoconstrictor drops immediately prior to each infusion and cooling eye pads during the infusion to reduce the risk of ocular AEs (Seagen Inc., 2023a,b). These preventative measures were associated with a reduced frequency and severity of ocular AEs, including conjunctivitis, in the Phase 1–2 trial of tisotumab vedotin (de Bono et al., 2019). However, these preventative measures were of limited effectiveness for preventing corneal AEs, including keratopathy, in a Phase 1 trial of tusamitamab ravtansine in patients with advanced solid tumors (Gazzah et al., 2022). Cooling eye masks were also used prior to belantamab mafodotin infusions in DREAMM-2 (Lonial et al., 2020), but similarly, the efficacy of this approach is uncertain and it should be used with discretion (Wahab et al., 2021). Data from a Phase 1/2 study of praluzatamab ravtansine in patients with advanced solid tumors suggested that ocular prophylaxis (i.e., vasoconstrictors, corticosteroids, artificial tears) had some effectiveness in preventing ocular AEs, given that more ocular events were reported in patients who did not versus patients who did receive prophylactic medications (Boni et al., 2022).

4.2. *Monitoring symptomatic patients*

Patients with ocular symptoms that do not resolve or worsen should be followed with regular ocular examinations, including visual acuity and slit lamp assessments, conducted by an ophthalmologist throughout the course of ADC treatment. This approach is consistent with recommendations for ADCs such as belantamab mafodotin (European Medicines Agency, 2022b; GlaxoSmithKline, 2022), enfortumab vedotin (Agensys, Inc and Seagen Inc, 2023; European Medicines Agency, 2022d), mirvetuximab soravtansine (ImmunoGen, Inc., 2022), and tisotumab vedotin (Seagen Inc., 2023a,b) (Table 4). Examples of ADC-related ocular lesions in slit-lamp examination are shown in Fig. 3. However, the optimal schedule for these examinations likely varies among different ADCs and must be carefully balanced against the severity of ocular AEs, the underlying cancer treatment, and the impact on the patient's quality of life due to the need for repetitive examinations.

Mitigating the side effects of ADCs is crucial to improving patient outcomes and treatment efficacy. A stepladder approach is recommended, beginning with the use of lubricants to alleviate mucosal irritation and discomfort. The use of steroids, either as primary or secondary prophylaxis, plays a debated role in managing inflammatory responses associated with ADC therapy. The decrease in epithelial turnover and thinning of the corneal epithelium, generally associated with topical steroid application, may influence visual symptoms reported by patients, particularly in cases of superficial microcystic epithelial changes (MEC). Depending on their state of centripetal progression, epithelial thickenings associated with MEC may induce temporary myopia (peripheral lesions), hyperopia (central lesions), reduced vision, and photophobia. The effects of topical steroid application, depending on ocular surface, inflammation, and corneal semiology, requires additional investigation.

To further mitigate side effects, techniques that reduce blood flow, such as applying a cool patch or using vasoconstrictors, can theoretically minimize localized adverse effects by decreasing the diffusion of ADCs through limbal terminal vasculature. Among vasoconstrictive agents, corticosteroids, phenylephrine, and brimonidine have been evaluated in clinical trials. Additionally, adjusting the administration protocol through dose delay and dose reduction strategies ensures that patients maintain tolerable exposure levels, thereby reducing related toxicity. In severe cases, the permanent discontinuation of ADC treatment might be

Table 4
Recommended ocular examination and monitoring protocols for ADC and associated AEs.

Study/Drug	Condition	Ocular AEs	Dose Modification	Sources
Belantamab Mafodotin (DREAMM-2)	Relapsed/ Refractory Multiple Myeloma	Keratopathy	• Dose delays in 48% of patients • Dose reductions in 27% • 3% discontinued treatment • Withhold for Grade ≥2 keratopathy • Resume at 1.9 mg/kg or discontinue for worsening symptoms	(European Medicines Agency, 2022b; GlaxoSmithKline, 2022; Lonial et al., 2020; Lonial et al., 2021)
Mirvetuximab Soravtansine (FORWARD I)	Platinum-resistant Ovarian Cancer	Superficial keratitis, corneal defects, ulcer, stromal opacity, reduced BCVA	• Dose modification in 20% of patients • Withhold for confluent superficial keratitis or BCVA reduction • Resume at same/reduced dose • Discontinue for corneal perforation	(Moore et al., 2021) (ImmunoGen, Inc., 2022).
Tisotumab Vedotin (InnovaTV 201)	Advanced/ Metastatic Solid Tumors	Conjunctivitis	• Withhold until improvement in conjunctivitis (43% of patients) • Resume at reduced dose for Grade ≥3 conjunctivitis • Withhold for confluent superficial keratitis • Discontinue for recurrent severe keratitis or perforation	(de Bono et al., 2019) (Kim et al., 2022; Seagen Inc., 2023b)
Tusamitamab Ravtansine	CEACAM5-positive NSCLC	Keratopathy, Keratitis	• Dose delay in 7/11 patients with keratopathy or keratitis • No discontinuations due to corneal AEs	Ricordel et al. (2022)
Belantamab Mafodotin (Real-World)	Relapsed/ Refractory Multiple Myeloma	Keratopathy	• 14% permanently discontinued • 11% dose reduction • 70% progression within 3 months for those who discontinued • Improved progression-free survival for those who restarted treatment	(Abeykoon et al., 2022) Mohan et al. (2022)
Tusamitamab Ravtansine (Phase 1)	Advanced Solid Tumors	Keratopathy, Keratitis	• Use corticosteroid-containing ocular drugs	Gazzah et al. (2022)
Anetumab Ravtansine + Pegylated Liposomal Doxorubicin	Platinum-resistant Ovarian Cancer	Corneal epithelial changes	• Reversible and managed with lubricating or corticosteroid eye drops	Santin et al. (2023)
Sodium Thiosulfate (BYON5667)	Metastatic Breast Cancer	Ocular AEs	• Ongoing study investigating eye drops for reducing ocular AEs	NCT04983238

ADC, antibody-drug conjugates; AE, adverse event; BCVA, best-corrected visual acuity; NSCLC, non-small cell lung cancer.

necessary to prevent potentially irreversible complications. These measures collectively help balance the potent therapeutic benefits of ADCs with an improved safety profile for patients undergoing cancer treatment.

4.3. Modification of ADC therapy

Several clinical studies have shown that ocular AEs associated with ADCs can be managed with dose modifications, though specific guidelines vary by ADC type. In the Phase 2 DREAMM-2 study of belantamab mafodotin in RRMM, 48% of patients experienced dose delays and 27% required dose reductions due to keratopathy, with 3% discontinuing treatmentdue to AEs (Lonial et al., 2020). Treatment to be withheld in patients with Grade ≥2 keratopathy until corneal or best-corrected visual acuity (BCVA) improved to Grade 1 or resolved, then resumed at a reduced dose, or permanently discontinued if symptoms worsened (European Medicines Agency, 2022b; GlaxoSmithKline, 2022; Lonial et al., 2020; Lonial et al., 2021). However, BCVA may not be reliable in early keratopathy stages, as microcysts can form peripherally without impacting visual acuity (Farooq et al., 2020). Reduced vision such as myopic shift may indicate the migration (and/or accumulation) of MECs from the peripheral to the central cornea (Chauver et al. Use of refractive shift in patients treated by belantamab mafodotin for follow up. Manuscript submitted).

In the Phase 3 FORWARD I trial of mirvetuximab soravtansine in platinum-resistant ovarian cancer, ocular AEs, including keratopathy, led to dose delays or modifications in 20% of patients (Moore et al., 2021). The US prescribing information recommends withholding mirvetuximab soravtansine for patients with significant corneal issues until improvement or resolution, then resuming at the same or a reduced dose. Treatment should be permanently discontinue in case of corneal perforation (ImmunoGen, Inc., 2022).

ADC treatment may require suspension or adjustment until ocular symptoms improve, as seen in the Phase 1–2 InnovaTV 201 study of tisotumab vedotin in patients with advanced or metastatic solid tumors (de Bono et al., 2019). Treatment was withheld in all cases of conjunctivitis (43%) and resumed at a reduced dose in those with Grade ≥3 conjunctivitis (3%) (de Bono et al., 2019). The US prescribing information recommends withholding treatment for keratitis until symptoms improve, followed by dose reduction, with permanent discontinuation after recurrent or severe keratitis (Kim et al., 2022; Seagen Inc., 2023a, b).

In a dose-expansion study of tusamitamab ravtansine in CEACAM5-positive NSCLC, 7 of 11 patients required dose delays (with or without reduction) for keratopathy or keratitis, but none discontinued treatment due to these AEs (Ricordel et al., 2022).

Permanent discontinuation of ADCs due to ocular AEs can significantly impact patient outcomes. In real-world analysis of 38 patients with RRMM, 14% permanently discontinued and 11% reduced the dose of belantamab mafodotin due to ocular AEs, with 70% progressing within a median of 3 month (Abeykoon et al., 2022), Another study of 56 patients with RRMM reported treatment interruption due to keratopathy

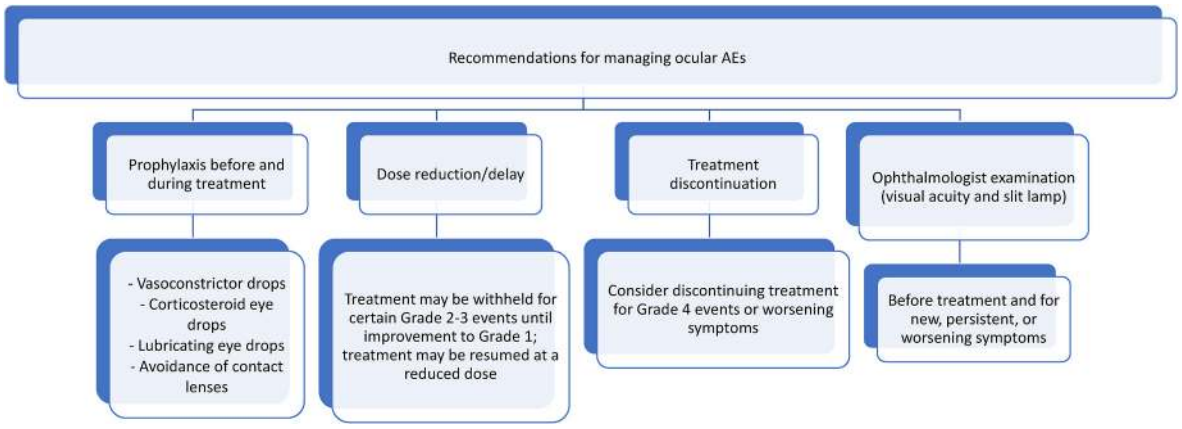

Fig. 6. Recommendations for managing ocular adverse events (Agensys, Inc and Seagen Inc, 2023; GlaxoSmithKline, 2022; ImmunoGen, Inc., 2022; Lonial et al., 2020; Seagen Inc., 2023b).

in 55% of those receiving belantamab mafodotin (Mohan et al., 2022). Patients who restarted belantamab mafodotin (n = 16) had significantly improved progression-free survival than those who permanently discontinued treatment (n = 13) [10 vs 4 months; $P = 0.032$] (Mohan et al., 2022).

Some ocular AEs may be managed with ophthalmic preparations. In the Phase 1 study of tusamitamab ravtansine in patients with advanced solid tumors, corticosteroid-containing ocular drugs were recommended for patients who developed keratopathy/keratitis (Gazzah et al., 2022). In a Phase 1b study of anetumab ravtansine plus pegylated liposomal doxorubicin in platinum-resistant ovarian cancer, corneal changes were reversible with lubricating or corticosteroid drops (Santin et al., 2023). An ongoing Phase 1/2 study is evaluating sodium thiosulfate (BYON5667) eye drops to reduce ocular AEs in patients with metastatic breast cancer receiving trastuzumab duocarmazine with results pending (NCT04983238). To provide a clear and practical resource for ophthalmologists, Table 4 summarizes the recommended ocular examination and monitoring protocols for these ADCs.

4.4. Patient-reported outcomes

Two patient-reported outcomes tools have been used to assess HRQoL in relation to ADC use and ocular AEs: the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25) and the Ocular Surface Disease Index (OSDI) (Mangione et al., 2001; Schiffman et al., 2000). The NEI-VFQ-25 is a validated questionnaire that assesses general health, general vision, near/distance vision, driving, peripheral vision, color vision, ocular pain, and vision-related role limitations, as well as dependency, social functioning, and mental health (Mangione et al., 2001). Using the NEI-VFQ-25, a recent study has shown that visual impairment or blindness is associated with reduced vision-related HRQoL (Asimadu et al., 2023), highlighting the need to effectively mitigate and manage any ocular AEs that occur during treatment with an ADC.

The OSDI is a reliable and valid tool for assessing the severity and frequency of dry eye symptoms and their impact on vision-related functioning and can be used as an endpoint in clinical trials (Schiffman et al., 2000). In the Phase 2 DREAMM-2 study in patients with RRMM, which used the NEI-VFQ-25 and OSDI to assess vision-related HRQoL, a clinically meaningful (≥12.5-point) worsening in the OSDI vision-related functioning domain was reported by approximately 50% of patients during treatment with belantamab mafodotin. Despite worsening ocular symptoms, however, the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ-C30) data suggest that overall HRQoL and patient functioning remained stable during belantamab mafodotin treatment (Popat et al., 2020).

5. Recommendations and conclusions

ADCs are a valuable therapeutic option for many cancers and are likely to be used with increasing frequency in the future. Although they are designed to minimize systemic toxicity due to off-target effects, some of these therapies are associated with ocular AEs. Moderate loss of visual acuity or blurred vision may be an early symptom of ADC-related ocular AEs, and ophthalmologic examinations for persistent or worsening symptoms during treatment is advisable to decipher the nature and severity of these AEs as early as possible (Fig. 6). In the case of moderate loss of visual acuity as a symptom of ADC-related corneal AEs, oncologists should consider dose modification (reduction or delay) and, in collaboration with ophthalmologists, the use of ocular topical treatments to manage ocular symptoms (Fig. 6). However, there are limited data concerning the effectiveness of the strategies implemented to minimize and mitigate these ocular AEs, emphasizing the need for the involvement of eye-care providers in the network of anti-cancer drug prescribers, especially for patients receiving ADC-based treatment. In this setting, ophthalmologists play an essential role in the detection, mitigation, and management of these ocular AEs. Unfortunately, access to ophthalmologists remains a global issue, especially among lower- and middle-income populations, with multiple barriers contributing to this suboptimal access, including approachability, acceptability, affordability, and availability (Marmamula et al., 2023). Improving access to ophthalmology care is crucial for patients with ADC-related ocular AEs, as these patients should be seen within a few days of the occurrence of ocular AEs. Ideally, organizing a network of ophthalmologists and other eye care professionals who would be available as needed for these patients would help address ocular issues in a timely manner.

In line with ADC-specific guidance, referral for ophthalmologic assessment should be considered before the start of treatment. However, access to ophthalmologists is sometimes limited, and in real-world clinical practice referral to an ophthalmologist when ocular symptoms develop or worsen may be sufficient to help differentiate ADC-related ocular AEs from those from other causes. Therefore, an improved specialized follow-up is advised when increased frequency and intensity of specific ADC therapies' ocular AEs are reported. However, as mentioned previously, access to ophthalmologic care remains a barrier and necessitates a network of ophthalmologists who would be readily available for these patients.

Although the product labelling for certain approved ADCs includes guidance regarding dose modification for managing ocular AEs, these recommendations are specific to the individual ADC agent, and labelling for other ADCs does not clearly specify what other ophthalmologic treatments should be used in conjunction with these dose modifications. Thus, ophthalmologists have an important role to play in careful adherence to recommended eye care and the administration of

appropriate treatments when ocular AEs occur to limit sequelae.

CRediT authorship contribution statement

Eric E. Gabison: Writing – review & editing, Conceptualization. **Antoine Rousseau:** Writing – review & editing, Data curation, Conceptualization. **Marc Labetoulle:** Writing – review & editing. **Anas Gazzah:** Writing – review & editing. **Benjamin Besse:** Writing – review & editing.

Data availability

No data was used for the research described in the article.

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