Br J Dermatol 2024; **00**:1–21
https://doi.org/10.1093/bjd/ljae344
Advance access publication date: 5 September 2024

BJD
British Journal of Dermatology
Guidelines

An expert consensus on managing dupilumab-related ocular surface disorders in people with atopic dermatitis 2024

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This expert consensus paper was prepared on behalf of the British Association of Dermatologists (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines subcommittee, and the Royal College of Ophthalmologists Bowman Club. Members of the Clinical Standards Unit and Bowman Club who have contributed are SL Chua (Chair, Therapy & Guidelines subcommittee), SB Kaye (Chair, Bowman Club), Helen Frow, Gorav Wali, Ravi Ramessur, Navpreet Dhillon, David Spokes, Frank Larkin, S Seddk Tawfik (BAD Guideline Research Fellow), C Wang (BAD Information Scientist), S Tumbeva (BAD Clinical Standards Project Coordinator) and MF Mohd Mustapa (BAD Director Clinical Standards).

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Abstract

Atopic dermatitis (AD) is the most common inflammatory skin condition and affects people of all ages. New therapies, including the monoclonal antibody therapy dupilumab, offer excellent efficacy. However, in clinical trials, and emphasized in real-world observations, an unexpected increased frequency of ocular adverse effects has become apparent. The effectiveness of dupilumab and the unpredictability of ocular adverse effects mean that clinicians need guidance on counselling patients prior to treatment and on managing them if adverse effects arise. The British Association of Dermatologists (BAD) and Royal College of Ophthalmologists collaborated on this consensus guidance on managing dupilumab-related ocular surface disorders (DROSD). A multidisciplinary group was formed of adult and paediatric dermatologists and ophthalmologists with expertise in DROSD, patient representatives and the BAD Clinical Standards Unit. A literature search was conducted and the results reviewed. All recommendations were reviewed, discussed and voted on. The recommendations pertain to dermatology and ophthalmology management, and apply to people of all ages, unless otherwise stated. Importantly, initiation of dupilumab for AD

Accepted: 30 July 2024

should not be delayed for most eye disorders except acute new problems (e.g. infections) or potentially severe conditions (e.g. a history of corneal transplant; ophthalmology advice should be sought first). There is insufficient evidence to recommend lubricant drops prophylactically. Dermatologists should assess eye complaints to diagnose DROSD; a severity grading system is provided. DROSD management differs slightly in those aged < 7 years, as ocular complications may affect neuro-ocular development. Therefore, irrespectively of DROSD severity, this population should be referred for ophthalmology advice. In those aged ≥ 7 years, dermatologists should feel confident to trial treatment and reserve ophthalmology advice for severe or nonresponding cases. Discussion about dupilumab withdrawal should be prompted by a significant impact on quality of life, threat to sight, or other complications. Although dupilumab is a highly effective agent for treating AD, the risk of ocular adverse effects should not inhibit clinicians or patients from using it, but clinicians should be aware of them. If a patient develops DROSD, there are clear pathways to assess severity and offer initial management. Where this is ineffective, dermatologists should assess the urgency and seek advice from or initiate referral to ophthalmology. While the evidence reviewed for these guidelines reflects the extensive literature on dupilumab, we believe our advice has relevance for ocular surface disorders in patients with AD treated with tralokinumab and lebrikizumab.

Purpose and scope

The main objectives of this expert consensus paper are as follows:

- To describe the types of ocular surface disorders observed with dupilumab therapy for atopic dermatitis (AD).
- To define the importance of ocular surface disorders in the UK including a review of the current state of knowledge of the prevalence of ocular surface disorders observed with dupilumab therapy for AD.
- To characterize a pathway for clinicians to follow, based on the UK healthcare setting, when advising patients prior to commencing dupilumab therapy for AD.
- To characterize a pathway for clinicians to follow, based on the UK healthcare setting, when managing patients on dupilumab therapy for AD who develop ocular surface disorders.

This review and recommendations are aimed to support dermatologists and ophthalmologists in managing their patients.

A detailed review of pathogenesis was excluded from the scope of this expert consensus paper, to enable a focus on evidence-based and pragmatic guidance for working clinicians.

Methods

A call for clinical experts was made to members of the British Association of Dermatologists (BAD) to join the BAD's Dupilumab Ocular Complications Working Group (DOCWG). Participants were selected following application by open invitation to members of the BAD and nominations provided by the Royal College of Ophthalmologists. All applicants were asked to provide declarations of interest, and the final group was selected, with weighting to provide a broad range of experience and balance between ophthalmology, dermatology, paediatrics and adult management. A patient representative was sought and was involved throughout the development of the manuscript.

All meetings were conducted online between May 2022 and March 2024, with group members designated to appropriate subgroups (including paediatrics, adults, ophthalmological management) to lead the review of their respective sections. The DOCWG is made up of consultant dermatologists (MRA-J, SJB, CF, ADI, GAJ, SML, PL, D'OK, GP, AEP, MS, RTW), consultant ophthalmologists (PH, S Rauz, S Robbie, SKG), a trainee dermatologist (D'OD), a trainee ophthalmologist (ML), a patient representative (AP) and a technical team consisting of an information scientist (CW), a project coordinator (ST) and a project manager (MFMM) providing methodological, technical and administrative support.

A literature search was undertaken on 5 July 2023 to identify relevant publications from PubMed to capture dupilumab, ocular surface diseases and ocular diagnoses (Appendix S1; see Supporting Information). Systematic and nonsystematic reviews of comparative and noncomparative studies (clinical trials and real-world evidence), as well as individual studies cited within them, were identified for consideration for inclusion and analyses. All recommendations were reviewed, discussed and voted on (via a yes/no option for each recommendation) independently by all clinicians and patient representative on the DOCWG, with 100% agreement on the clinical recommendations.

All manuscript drafts were shared with all DOCWG members for review. Comments on the draft manuscript were also sought from the Bowman Club (Royal College of Ophthalmologists) and the Therapy & Guidelines subcommittee (BAD). These were then reviewed by DOCWG members, and the manuscript amended accordingly, before the updated draft version was circulated to the wider BAD and Royal College of Ophthalmologists memberships and industry stakeholders for comment. Final amendments were approved by the Bowman Club and the Therapy & Guidelines subcommittee before submission for publication. Throughout the process, anonymous comments were not allowed, and no incentives were provided to participate in the process at any stage.

The strength of recommendation rating is expressed by the wording and symbols utilized in BAD clinical guidelines, shown in Table 1.

Summary of recommendations

The following recommendations and ratings are based on available clinical trials and real-world data and were agreed upon following extensive discussion by members of the DOCWG, with representatives from the BAD and Royal College of Ophthalmologists, and a patient representative from Eczema Outreach Support. The DOCWG is aware of the lack of high-quality evidence for some recommendations. A Good Practice Point (GPP) recommendation is derived from expert consensus. Strong recommendations marked with an asterisk (*) are based on the limited or

Table 1 Strength of recommendation rating

Strength	Wording	Symbols	Definition
Strong recommendation *for* the use of an intervention	'Offer' (or similar, e.g. 'use', 'provide', 'take', 'investigate', etc.)	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention while only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policymakers, it would be a useful performance indicator
Weak recommendation *for* the use of an intervention	'Consider'	↑	Risks and benefits of the intervention are finely balanced; most patients would choose the intervention, but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policymakers it would be a poor performance indicator where variability in practice is expected
No recommendation		Θ	Insufficient evidence to support any recommendation
Strong recommendation *against* the use of an intervention	'Do not offer'	↓↓	Risks of the intervention outweigh the benefits; most patients would *not* choose the intervention while only a small proportion would; for clinicians, most of their patients would *not* receive the intervention

lower-certainty evidence available and consensus based on specialist experience.

Recommendations are subdivided into those for dermatology, ophthalmology and future research. All recommendations are for people of all age groups ('people') receiving dupilumab therapy for AD, unless stated otherwise (e.g. children aged 0–12 years, young people aged 13–17 years).

Dermatology

R1 (↑↑) Offer* prophylactic use of preservative-free ocular lubricants (Table 2) to people with current or pre-existing corneal or conjunctival eye disease managed in ophthalmology prior to commencing dupilumab therapy (Table 3 and Figure 1a).

R2 (GPP) Refer to ophthalmology (standard/routine referral pathway) people with significant current or chronic corneal or conjunctival eye disease who are commencing dupilumab therapy (Figure 1a).

R3 (GPP) Delay commencement of dupilumab therapy for people with a history of corneal transplant until discussion with ophthalmology, or for those with reversable acute eye conditions (e.g. infectious conjunctivitis) until after resolution (Figure 1a).

Θ There is insufficient evidence to recommend ocular lubricants prophylactically for people with no current or pre-existing eye disease prior to commencement of dupilumab therapy.

R4 (GPP) Manage people with unilateral eye symptoms via existing management pathways as these are unlikely to represent DROSD.[1,2]

R5 (GPP) Classify DROSD severity as mild, moderate or severe based on the degree of redness and symptomatology (Figure 2).

R6 (↑↑) Urgently refer* to ophthalmology (within 24 h) people with DROSD as recommended by the RAPID acronym (Table 4 and Figure 1b).

Redness plus any of the following:

- **A**cuity loss or worsening
- **P**ain (i.e. ocular pain, moderate or severe of new onset, more than irritation or foreign body sensation)
- **I**ntolerance of light (sensitivity/photophobia)
- **D**amaged cornea visible or opacity.

R7 (GPP) For children (< 7 years) on dupilumab therapy with mild-to-moderate ocular symptoms (intermittent symptoms, foreign body sensation or eye rubbing) or mild and intermittent conjunctival injection or eyelid swelling (both eyes), commence preservative-free ocular lubricants and refer to ophthalmology for assessment within 4 weeks of referral.

Table 2 Ocular lubricants appropriate for people of all ages as recommended based on the severity of dupilumab-related ocular surface disorders (DROSD). Prescribe three to four times daily

Active ingredient	DROSD severity
Hypromellose PF	Mild
Sodium hyaluronate 0.1–0.2% PF	Moderate
Carmellose 0.5–1% PF	Moderate
Sodium hyaluronate 0.15% with trehalose PF	Moderate
Sodium hyaluronate 0.3–0.4% PF	Severe
Paraffin-based eye ointments PF[a]	Severe
Lipid/oil/omega-3-containing emulsions or perfluorohexyloctanes[b]	Unknown
Liposomal sprays[b]	Unknown

PF, preservative free. [a]Usually reserved for night-time usage. [b]Available over the counter.

Table 3 Risk factors for dupilumab-related ocular surface disorders (DROSD) in patients with atopic dermatitis (AD) commencing dupilumab, subdivided into those for whom there is evidence (left column) and those for whom there is theoretical rationale but no reproduced evidence to date (right column)

Risk factors for DROSD	Other possible risk factors for DROSD
• AD (as opposed to other indications) • Ophthalmology attendance previously for ocular surface disorder (especially pre-existing dry eye disease *and* keratitis)	• Higher baseline AD severity and markers, e.g. thymus and activation-regulated chemokine (TARC) • Elevated eosinophil count at baseline • Eyelid or facial eczema • Elevated total IgE at baseline

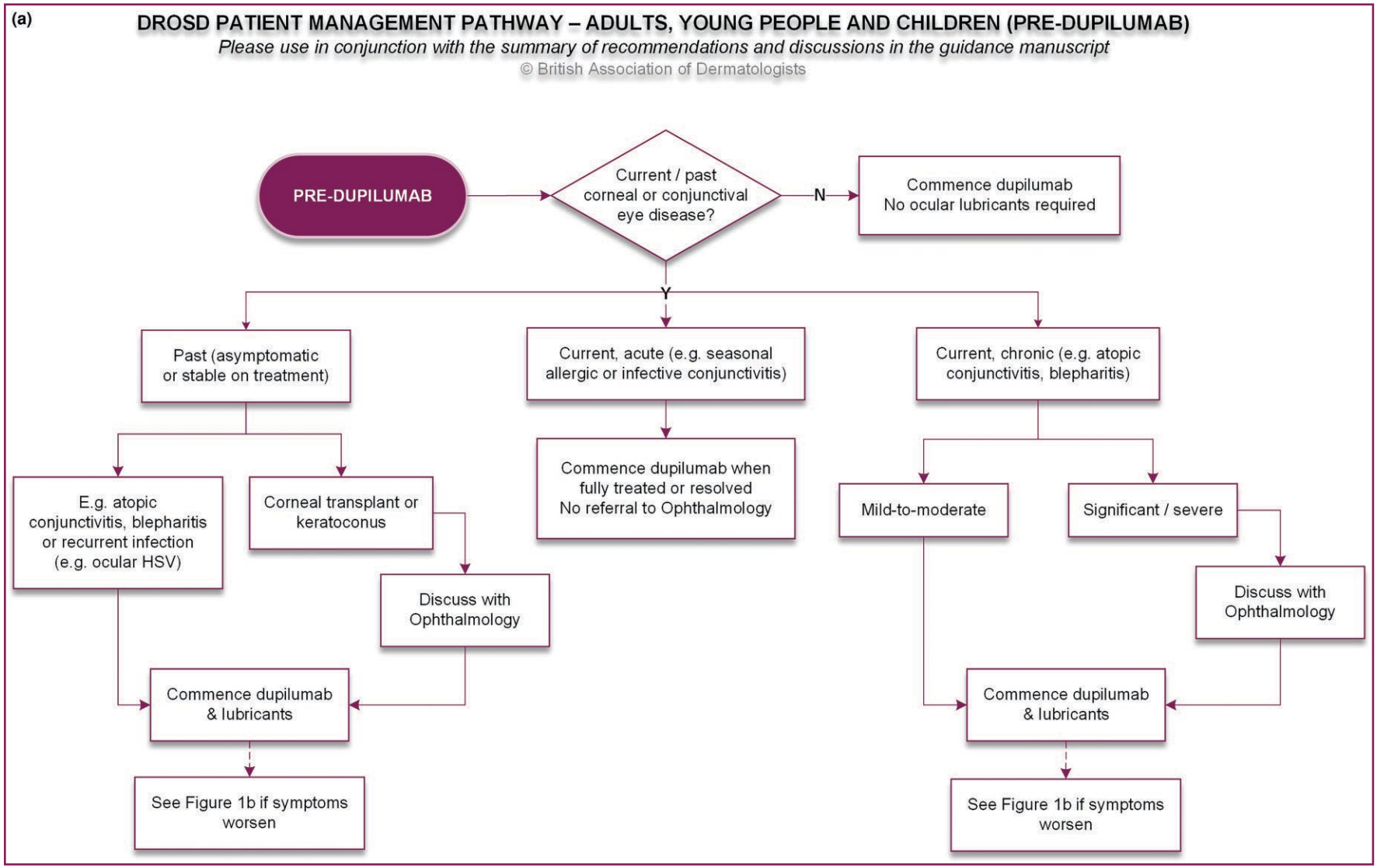

Figure 1 Managementof (a) pretreatment risks and (b) dupilumab-related ocular surface disorders (DROSD) by dermatologists in adults, children and young people. Individuals without ocular signs or symptoms do not require ocular monitoring, but new symptoms should prompt initiation of the pathway. Redness is usually bilateral in DROSD. Unilateral redness should prompt consideration of other causes. Red flags are defined according to the RAPID acronym: **r**edness, **a**cuity loss, **p**ain, **i**ntolerance to light, **d**amage to cornea. Ocular pain is defined as moderate or severe, of new onset and more than irritation or foreign body sensation (Table 4). Corneal damage is determined by inspection for evidence of uptake of topical fluorescein, or visible evidence of corneal surface ulceration, haze, opacity or purulent discharge. While signs of corneal damage are important red flag features, they are challenging to detect on examination by a nonspecialist. Such findings would normally be accompanied by other red flags, so redness (either bilateral or unilateral) with any other red flag should prompt discussion with the local ophthalmology team, if possible, and emergency referral (< 24 h) or attendance at eye casualty (Table 4). Severity of redness in DROSD may be defined as mild, moderate or severe (Figure 2). In adults, mild-to-moderate cases should have treatment initiated and reviewed by dermatologists. In cases requiring topical tacrolimus treatment, or those classified as severe at the outset, treatment should be commenced but a review by ophthalmology within 4 weeks is recommended. In children, those aged < 7 years still have plasticity of visual development pathways, and therefore any changes should be discussed with ophthalmology before treatment is initiated. In children aged ≥ 7 years, simple treatment can be initiated by dermatology; however, unlike in adults, progression up the treatment ladder requires ophthalmology assessment. *For severity assessment, see Figure 2. ASAP, as soon as possible; bd, twice daily; HSV, herpes simplex virus; od, once daily; qds, four times daily. (*Continued*)

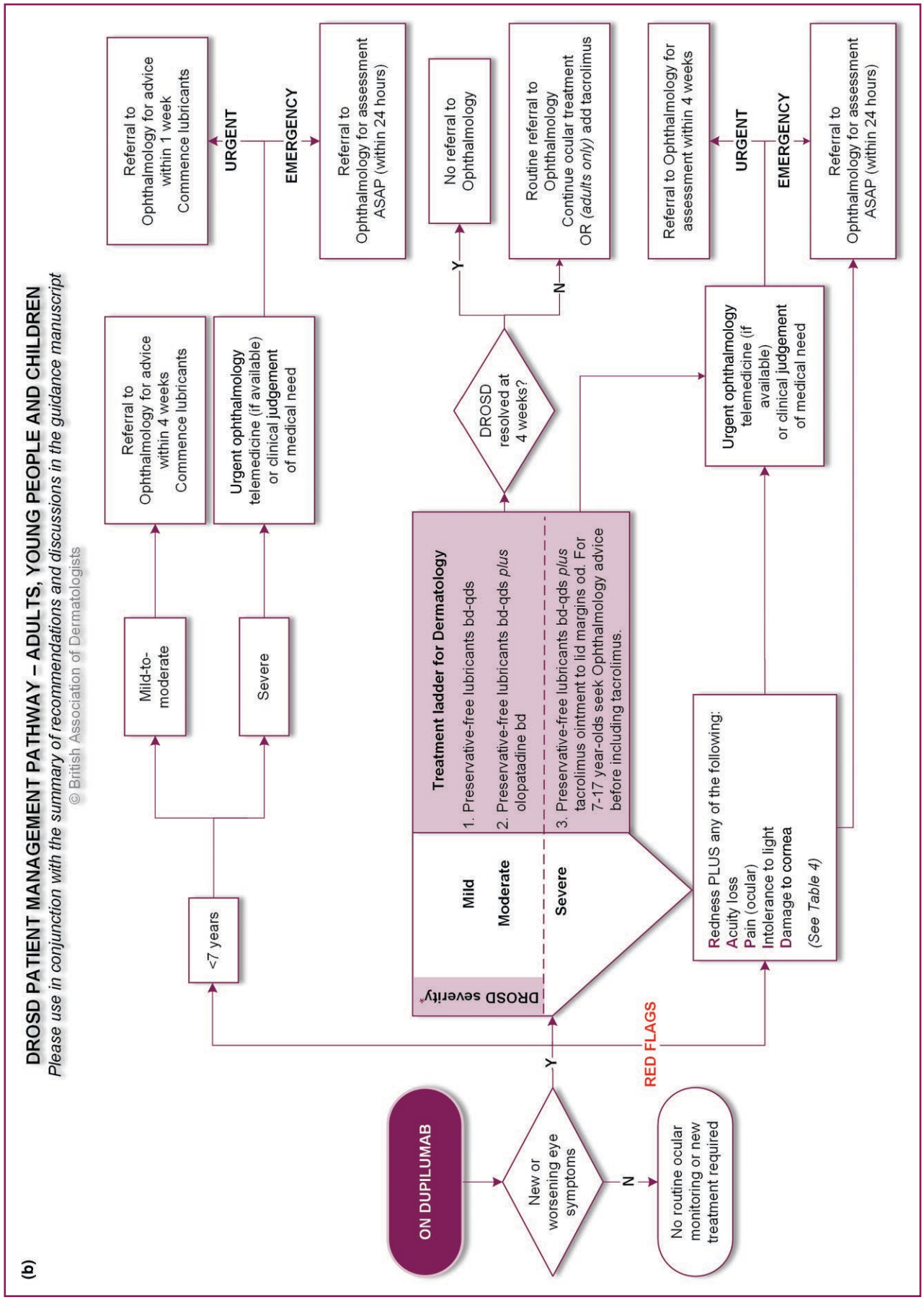

Figure 1 (*Continued*)

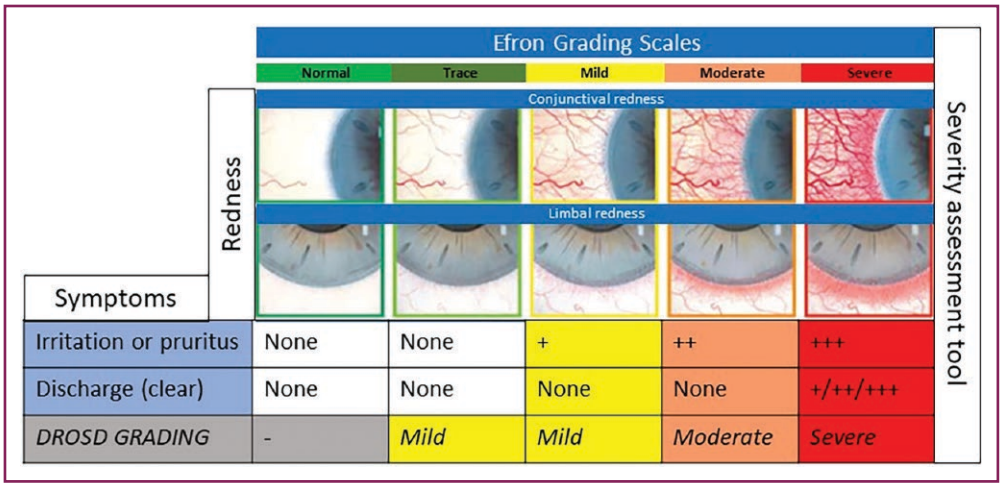

Figure 2 Severity assessment of dupilumab-related ocular surface disorders (DROSD) by dermatologists for those aged ≥ 7 years. Assessment of the severity of DROSD by assessing ocular redness (Efron grading system)[101,102] and symptoms. Importantly, redness and symptomatology may not always correlate. Therefore, classification of DROSD as mild, moderate or severe is based on the most severe finding. For example, an individual with moderate ocular redness, but no symptoms, would be classified as having moderate DROSD. Children aged < 7 years should be discussed with ophthalmology for severity grading. This figure is reproduced, with permission from Elsevier, from the supplement to the book *Contact Lens Complications*, 2nd edn, ISBN: 9780750655347, 2004, Efron.[110]

For severe cases refer to ophthalmology for assessment within 1 week of referral.

R8 (GPP) Refer children and young people (7–17 years) with mild-to-moderate DROSD to ophthalmology (standard/routine referral pathway) who do not respond to topical lubrication or antihistamine eyedrops. Initiate or continue topical lubricant therapy (Figure 1b).

R9 (GPP) Refer children and young people (7–17 years) with severe DROSD to ophthalmology, for assessment as an emergency (i.e. within 24 h) or urgent assessment within 4 weeks of the referral, as per clinical judgement. Initiate or continue topical lubricant therapy (Figure 1b).

R10 (GPP) Refer adults with mild-to-moderate DROSD who do not respond to topical treatment and lid hygiene to ophthalmology (standard/routine referral pathway). Initiate or continue topical lubricant therapy (Figure 1b).

R11 (GPP) Refer adults with severe DROSD to ophthalmology, for assessment as an emergency (i.e. within 24 h) or urgent assessment (within 4 weeks) of referral, as per clinical judgement. Initiate or continue topical therapy (Figure 1b).

R12 (↑↑) Offer* adults, young people and children (> 7 years) with mild, moderate or severe DROSD preservative-free ocular lubricants (Table 2) as first-line treatment.

R13 (↑↑) Offer* adults, young people and children (> 7 years) with DROSD topical antihistamine eyedrops (Table 5) as a second-line treatment option in addition to ocular lubricants if ocular lubricants alone are ineffective.

R14 (GPP) Offer adults with moderate-to-severe DROSD tacrolimus 0.1% ointment (applied once daily to the lid margins on a trial basis for 4 weeks), in addition to ocular lubricants, if lubricants and/or antihistamines have been ineffective. Refer to ophthalmology for assessment within 4 weeks for those applying tacrolimus ointment to lid margins.

R15 (↑↑) Initiate* prompt patient-centred discussion of possible withdrawal of dupilumab treatment, including the patient (or carer), dermatology and ophthalmology for those with DROSD when ophthalmological assessment confirms:

- Significant risk to visual acuity from inadequately controlled DROSD inflammation (e.g. progressive conjunctival cicatrization).

Table 4 The RAPID algorithm

Symptom/sign	Descriptor	Must be present	Score
Redness (Efron grading)[101,102]	Mild, moderate or severe bulbar redness (conjunctival)	Yes	1
Acuity loss	Worsened vision. Assessed by the patient or physician. No need for formal Snellen examination	No	1
Pain	Ocular pain, moderate or severe of new onset, more than irritation or foreign body sensation	No	1
Intolerance of light	Photophobia	No	1
Damaged cornea	Visible corneal ulceration, haze, opacity or purulent discharge	No	1

The RAPID algorithm was developed by the Dupilumab Ocular Complications Working Group for same-day referral of red flag ocular complications in those taking dupilumab. Ocular redness must be present. A score of 2 points or more, or unilateral red eye, warrants ophthalmological assessment within 24 h.

Table 5 Antihistamine approaches appropriate for people of all ages[59]

Active ingredient	Age (years)	Application	Common adverse effects
Mast cell stabilizers			
Sodium cromoglycate	All	4 times daily	Burning and stinging
Lodoxamide	> 4	4 times daily	Dry eye, discomfort, vision disorders
Antihistamines			
Antazoline with xylometazoline	> 12	2–3 times daily for 7 days	Drowsiness, eye irritation, headache, hyperhidrosis, hypertension, mydriasis, nausea, palpitations, vascular disorders
Azelastine hydrochloride	> 4	2–4 times daily	Mild transient irritation, bitter taste
Epinastine hydrochloride	> 12	2 times daily for up to 8 weeks	Burning
Ketotifen	> 3	2 times daily	Transient burning or stinging, punctate keratitis, punctate corneal epithelial erosion
Olopatadine	> 3	2 times daily for up to 4 months	Local irritation

- Significant risk of serious ocular adverse effects from requirement for prolonged ocular topical corticosteroid therapy (> 8 weeks).
- Significant loss of quality of life for the patient caused by inadequately controlled DROSD, for example as measured by Dermatology Life Quality Index (DLQI) or Children's DLQI, or Ocular Surface Disease Index (OSDI).

R16 (↑↑) Withdraw* dupilumab therapy from people with DROSD upon confirmation by ophthalmology of progressive loss of visual acuity that is unresponsive to treatment.

R17 (↑) Consider withdrawal of dupilumab therapy in people with progressive conjunctival cicatrization or scarring.

R18 (GPP) Consider referral for patch testing in people with DROSD unresponsive to topical treatment.

Ophthalmology

R19 (GPP) Review referrals from dermatology for patients with DROSD within the recommended timeframe (Table 6).

R20 (↑↑) Perform age-appropriate subjective and objective ocular assessments when patients are reviewed by ophthalmology (Table 7).

R21 (↑↑) Offer* topical lubricants to people with DROSD (Table 2).

Table 6 Ophthalmology first assessment timing for individuals who develop dupilumab-related ocular surface disorders (DROSD)

Age (years)	DROSD severity	Dermatology action at time of referral	Ophthalmology review
All	Red flags (Table 4)	Await ophthalmology advice	Within 24 h
< 7	All	Start topical treatment after ophthalmology advice	Within 4 weeks
7–17	Mild	Start topical treatment	Routine
7–17	Moderate-to-severe	Start topical treatment	Within 4 weeks
≥ 18	Mild	Start topical treatment	Routine
≥ 18	Moderate-to-severe	Start topical treatment	Within 4 weeks

Table 7 Ophthalmology assessment

Assessment (in approximate order of measurement)	Key findings	Adults	Children
Ocular Surface Disease Index score	Patient-reported outcome	Yes	Yes[a]
Visual acuity	Objective score	Yes	Yes[a]
Refraction	Cycloplegic/subjective	Not usually	Yes
Stereopsis and ocular alignment		Not usually	Yes
Eyelid margin	Lid wiper assessment	Yes	Yes
Slit lamp	Anterior segment and lacrimal puncti	Yes	Yes[a]
Assessment of lacrimal puncti	Punctal dilation and saline test	If indicated	Not usually
Fluorescein	Fluorescein dye test	If indicated	Yes
Tear film	Tear film breakup, epithelial erosions	Yes	Not usually
Conjunctiva	Inflammation, scarring	Yes	Yes
Cornea	Opacity (any cause), vascularization, thinning	Yes	Yes
Lens ± dilated pupil	Anterior/posterior cataract	Yes	Yes
Intraocular pressure	Objective measure	Yes	Yes[a]
Intraocular inflammation	Anterior chamber, vitreous	Yes	Yes
Retinal assessment	Indirect, slit lamp or fundus photos	If indicated	If indicated
Nerve	Cup-to-disc ratio	If indicated	If indicated
Corneal topography/tomography	Keratoconus assessment	If indicated	If indicated

[a]If age appropriate.

R22 (↑↑) Offer* topical antihistamines to people with mild or moderate DROSD if these have not been tried previously (Table 5).

R23 (↑↑) Offer* warm compresses to adults with the blepharitis subtype of DROSD (e.g. meibomian gland dysfunction).

R24 (↑↑) Offer* tacrolimus ointment for application to the lid margins to adults and children (> 7 years) with DROSD if this has not been tried previously.

R25 (↑↑) Avoid* tacrolimus ointment if this has been tried for 2–4 weeks (with appropriate directions) and has been ineffective, or if it has not been tolerated.

R26 (↑↑) Offer* short-term ocular topical corticosteroids (e.g. preservative-free dexamethasone 0.1%, prednisolone 0.5%, or hydrocortisone 0.335% eyedrops) to people with moderate-to-severe DROSD (if dermatology-initiated interventions are ineffective).

R27 (↑↑) Commence early introduction of corticosteroid-sparing agents (e.g. ciclosporin drops) in people with moderate-to-severe DROSD (see **R28**).

R28 (↑) Consider commencing an ocular topical corticosteroid-sparing agent (e.g. ciclosporin drops) at the same time as corticosteroid drops to facilitate corticosteroid tapering in people with DROSD.

R29 (↑↑) Offer* ocular topical ciclosporin to children and young people (4–17 years) with severe, DROSD-related vernal keratoconjunctivitis that has not improved despite treatment with standard topical therapy, in line with its marketing authorization.

R30 (↑↑) Offer* ocular topical ciclosporin to adults with DROSD-related severe, dry eye disease that has not improved despite treatment with ocular lubricants, in line with its marketing authorization.

R31 (GPP) Consider a combination of tacrolimus ointment and ciclosporin drops for people with treatment-resistant DROSD.

R32 (↑↑) Offer ongoing, regular supervision by an ophthalmologist for those on longer-term (> 8 weeks) corticosteroid eyedrop therapy (e.g. maximum twice-daily dosage of 0.1% dexamethasone) for people with DROSD where corticosteroid-sparing agents are ineffective or contraindicated, and dupilumab withdrawal is not advisable. Monitor patients as per routine guidelines for the use of ocular topical corticosteroids (including baseline retinal nerve fibre layer optical coherence tomography).

R33 (↑) Consider serum eyedrops (unlicensed) for people with DROSD refractory to licensed topical therapy after discussion with an ophthalmologist in a specialized centre commissioned to provide serum drops for patients with severe ocular surface disease.

Future research recommendations

The following list outlines some future research recommendations (FRRs). These FRRs were developed following review of the evidence (and any gaps identified), and formulation of the recommendations.

FRR1 Further investigation of the genetic predisposition and/or mechanistic factors that drive the development of DROSD.

FRR2 Investigation of the precise pathomechanism(s) of DROSD including the influence of ageing.

FRR3 Recruitment of cohorts of dupilumab-treated patients for observational studies to characterize the biomarkers for DROSD, complications and long-term prognosis.

FRR4 Randomized controlled trials evaluating the effect of interventions in preventing or reducing the risk of DROSD.

FRR5 Randomized controlled trials evaluating the effect of interventions to treat DROSD including the effect of reducing the dose of dupilumab therapy.

FRR6 Investigation of the most important risk factors for DROSD including differences between ethnicities and markers of social deprivation.

FRR7 Investigation of the potential for DROSD to cause long-term sequelae following cessation of dupilumab therapy.

FRR8 Investigation of the long-term outcome of subclinical or treated DROSD when dupilumab therapy is continued.

FRR9 Characterize the differences in treatment and response in children vs. adults with DROSD.

Algorithm

Figure 1 summarizes the key steps in managing (a) pretreatment risks and (b) DROSD by dermatologists in adults, young people and children.

Introduction

AD is a common, chronic, inflammatory skin condition that affects up to 25% of children and 10% of adults.[3,4] Of all those affected with AD, one-quarter will have moderate-to-severe disease; it is characterized by intense pruritus, which can be debilitating.[5,6] AD is frequently associated with other allergic disorders (e.g. asthma, hay fever), as well as skin infections and neuropsychological issues.

In the last decade, the increasing knowledge of the pathogenesis of AD has led to a narrowing focus for intervention in a few key molecular pathways. There is immunological skewing towards T helper 2 responses in AD, as shown

by an increased number of cells expressing interleukin (IL)-4, IL-5 and IL-13 in early lesional AD skin compared with nonlesional or control skin.[7,8] This at least partly explains the pathology of the disease: IL-4 and IL-13 downregulate filaggrin expression in keratinocytes, thereby contributing to epidermal barrier disruption.[9] Furthermore, IL-4 is known to downregulate expression of cutaneous defensins[10] and increase expression of bacterial adhesion molecules, both of which facilitate *Staphylococcus aureus* colonization in AD.[11,12]

Dupilumab is a fully human IgG4 monoclonal antibody that binds to the alpha subunit of the IL-4 receptor (IL-4Rα). IL-4Rα forms a heterodimer with the common γ chain to form an IL-4 receptor, or with IL-13Rα1 to form a receptor for IL-13. Therefore, dupilumab blocks signalling from both IL-4 and IL-13. Dupilumab has been licensed in Europe and the USA for the treatment of moderate-to-severe AD. In Europe and the UK, the licence is for adults and adolescents aged > 12 years who are candidates for systemic therapy, whereas in the USA, the drug is licensed for children aged > 6 months. This therapy has transformed the management of moderate-to-severe AD.

The effectiveness of dupilumab was shown in clinical trials of dupilumab vs. placebo: SOLO1 and SOLO2 ($n=671$ and $n=708$, respectively),[13] and dupilumab and topical corticosteroids vs. placebo and topical corticosteroids: LIBERTY AD CHRONOS and LIBERTY AD CAFÉ ($n=740$ and $n=325$, respectively).[14,15] In these studies, improvement in Investigator's Global Assessment (IGA) or achievement of EASI 75 (≥ 75% reduction in Eczema Area Severity Index score) was demonstrated clearly ($P<0.001$ in all studies). In practical terms, combination therapy with dupilumab and topical corticosteroids delivers EASI 75 in 63–64% of cases at 16 weeks. Additionally, significant improvements in itch, quality of life and sleep were noted. Since those studies, many real-world datasets have been published that demonstrated similar levels of efficacy in clinical practice, with a pooled EASI 75 of 59% at 16 weeks.[16]

The safety profile of dupilumab over more than 10 years of follow-up has been shown to be excellent. Of all the adverse effects reported, the most prevalent are ocular surface adverse events in treated patients. In clinical trials, this was shown to arise in 6–15% of adults treated with dupilumab vs. 0.9–10.9% in those exposed to placebo. However, in real-world data, 26.1% of patients developed conjunctivitis [95% confidence interval (CI) 17.8–35.4] among 908 patients with AD (14 studies),[17] and a higher proportion reported dry eyes. Significantly, 4.2% of patients discontinue dupilumab because of ocular complications.[17] Therefore, in clinical practice, management of ocular surface disorders is an important aspect of dupilumab prescribing. To date, there is no consensus for the management of ocular surface complications arising from dupilumab therapy.

1. Disorder name

During treatment with dupilumab there is an increased risk of eye problems. The cases reported to date are almost exclusively constrained to the surface of the eye. Within the group of reported conditions (Table 8), it is clear that many such eye problems are exacerbations of pre-existing atopic eye disease, but they can also be *de novo* development of well-recognized ocular surface disease. Conversely, some atopic eye disorders appear to improve with dupilumab treatment. To date, there is no definitive evidence of a novel disease induced by dupilumab. The current consensus among the DOCWG was that the eye problems experienced by patients on dupilumab are a group of established disorders rather than a single entity. Through a consensus voting procedure we elected to refer to these problems as 'dupilumab-related ocular surface disorders' (DROSD) to reflect the anatomical location and the heterogeneous group of eye diagnoses.

Table 8 Ocular diagnoses recorded by ophthalmologists in association with dupilumab therapy. Incidence rates are derived from synthesis of data from papers reviewed

Incidence	Ocular diagnosis
Common (approx. 85% of DROSD)	(Kerato)conjunctivitis (including atopic, follicular, papillary and vernal)
	Blepharitis
	Dry eye
	Meibomian gland dysfunction
	Keratitis (including marginal)
Infrequent (approx. 12.5% of DROSD)	Limbitis
	Cicatricial conjunctivitis
Rare (approx. 2.5% of DROSD)	Punctal stenosis
	Limbal epithelial stem cell deficiency
	Corneal ulceration
	Posterior scleritis
	Anterior and intermediate uveitis
	Placoid chorioretinitis
	Cystoid macular oedema

DROSD, dupilumab-related ocular surface disorders.

2. Anatomy of the ocular surface

Part of the ocular surface, the conjunctiva is a translucent mucous membrane. This membrane comprises conjunctival epithelial cells and underlying vascular stroma extending from the mucocutaneous junction at the eyelid margin to the corneal limbus, where it becomes continuous with the corneal epithelium. The transparent cornea, the other integral part of the ocular surface, is composed of cellular and noncellular components. The corneal epithelium is a highly regular, stratified squamous nonkeratinized epithelium, which comprises terminally differentiated epithelial cells centrally and a transitional epithelium at the limbus, housing the limbal epithelial stem cell niche that differentiates into corneal epithelium.

The corneal stroma forms a transparent structural framework of precisely organized collagen fibrils arranged in parallel bundles, surrounded by an extracellular matrix (glycosaminoglycans constitute keratan sulfate, chondroitin sulfate, dermatan sulfate and hyaluron) and keratocytes. Keratocytes are thought to be a form of mesenchymal stem cell involved in maintaining homeostasis. They have a critical role in corneal injury; when activated, they have the capability of transforming into fibroblasts and myofibroblasts.

The inner layer of the cornea is formed by the sodium-transporting endothelium, which regulates corneal water content by maintaining it in a relatively dehydrated state. The cornea and conjunctiva are coated by a complex tear film structure composed of an aqueous nutrient-rich

component (e.g. growth factors, vitamins, immunoglobulins, antimicrobial peptides) secreted mainly by the lacrimal glands. Negatively charged membrane-bound and soluble mucins synthesized by the conjunctival goblet cells render hydrophilic properties to the ocular surface, increasing the wettability and enabling the aqueous tears to spread across the surface of the eye.

The overlying layer of the tear film is predominantly lipid containing, produced by the meibomian glands arranged vertically in the eyelids with the opening orifices at the eyelid margin. Lipoproteins [lipocalin, lysozyme, surfactant proteins, nonpolar lipids and long-chain (*O*-acyl)-hydroxy fatty acids] spread across the ocular surface with each blink cycle, maintaining tear film stability and minimizing tear film evaporation.

3. Ocular surface disorders

Dysfunction (hereditary conditions) or destruction (from trauma, chemical injury, inflammation, autoimmune disease or neoplasia) can affect any part of the ocular surface (Figure 3). For example, damage to the limbal stem cells, termed limbal stem cell deficiency, leads to an invasion of conjunctival epithelium onto the corneal surface. Inflammation localized to the skin of the lid margin at the junction between skin of the outer lid margin (containing eyelashes) and free lid margin (site of meibomian glands) with the mucosal inner lid border (marginal conjunctiva) is termed anterior or posterior blepharitis or meibomian gland dysfunction (MGD). Inflammation of the conjunctiva is termed conjunctivitis, and inflammation of the cornea is termed keratitis. Inflammation affecting both the cornea and conjunctiva is frequently termed keratoconjunctivitis. All disorders can impact upon tear film integrity and give rise to aqueous-deficient, evaporative or mixed dry eyes.

Atopic eye disease is typically a chronic inflammatory keratoconjunctivitis. The underlying pathology is of goblet cell proliferation and epithelial infiltration of eosinophils and mast cells, followed by increased levels of T cells, T helper cells, macrophages and dendritic cells. In mild cases, there may be mild eyelid margin disease and conjunctivitis. In moderate cases, the eyelids and periorbital skin will have evidence of AD; the conjunctiva will be hyperaemic (red) and oedematous, characterized by a papillary tarsal conjunctival reaction. In severe forms of disease, a slowly progressive cicatrizing conjunctivitis, punctate epithelial corneal erosions, corneal vascularization and pannus formation occur, with high risk of corneal ulcers, infections and perforation (necessitating ocular surface reconstructive surgery).

Formation of cataracts is common among atopic individuals, and these are typically anterior capsular (frequently with calcification) or posterior subcapsular (frequently associated with topical corticosteroid use: creams, inhalers or drops). Patients with ocular surface disease are also at greater risk of herpes simplex keratitis or keratouveitis, which can be sight threatening.

Risk stratification in adults and children

1. When does DROSD occur?

In clinical trials and real-word studies, most cases of DROSD develop within the first 4 months of treatment.[18,19] However, later onset of DROSD can occur; in one case series, 7 of 13 patients with DROSD developed DROSD ≥ 150 days after treatment initiation.[20]

2. How common is DROSD?

The incidence of ocular surface disease has been recorded in preclinical trials, postmarketing surveillance reports, case reports and retrospective case series. Most data are derived from adult cohorts. In a meta-analysis of the reported publications in adults, the prevalence of ocular disorders in AD randomized clinical trials was noted to be lower (10.9%) than that identified in retrospective or observational cohorts (20.6–25.1%).[21]

Some heterogeneity in incidence rates of DROSD in adults has been observed in real-world datasets (with $n \geq 100$)

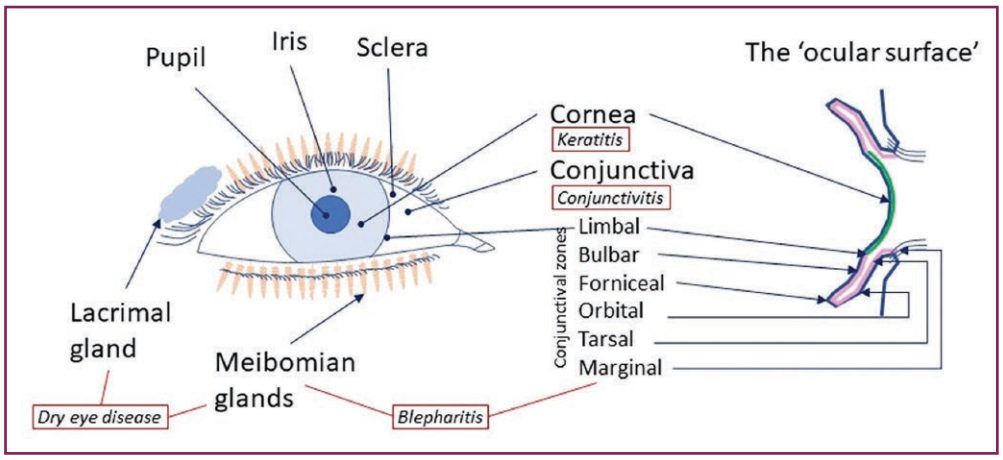

Figure 3 The ocular surface and associated disorders. Overlying the sclera is the conjunctival mucosa (pink), which together with the epithelia of the cornea (green) make up the ocular surface. Common ocular surface diseases are associated with dysfunction in specific areas of the ocular surface, including keratitis (cornea), conjunctivitis (any conjunctival zone), blepharitis (marginal conjunctiva and often meibomian gland dysfunction) and dry eye disease (lacrimal and meibomian gland dysfunction).

including the UK (32–42%),[22,23] France (13.3–18%),[24,25] Italy (11–12.2%),[26–28] Germany (29.8%),[29] the Netherlands (19.8–20.8%),[30,31] the USA (8.1%)[32] and South Korea (5%).[33] Whether such differences truly reflect evidence for genetic predisposition to DROSD remains uncertain. For example, in China, one study reported DROSD arising with a low prevalence of 2.59%,[34] whereas others have recorded 10.9–15%.[35,36]

3. Who is more likely to get DROSD?

Making a definitive assessment of DROSD risks based on the literature published to date is challenging due to significant heterogeneity in recording of baseline characteristics and the method by which DROSD was diagnosed (self-reported or based on ophthalmology or dermatology assessment).

The established risk of DROSD in patients with AD treated with dupilumab is not observed with its use in other clinical indications. Systematic reviews of randomized controlled trials identified comparable rates of ocular surface disease in placebo- and dupilumab-treated patients with asthma, chronic rhinosinusitis and eosinophilic oesophagitis.[18,21,37] In addition, a real-world analysis of a US prescription database identified an increased risk of ocular surface disease following commencement of dupilumab for patients with AD, but not with asthma.[38]

Some studies have suggested that the risk of DROSD increases with baseline eczema severity. However, although published data from a review of all patients treated with dupilumab in clinical trials (AD, $n=2629$) showed higher rates of DROSD per 100 person-years in cases with higher EASI or IGA at baseline, the differences were small and were not statistically significant.[18] A second study from a prospective, observational cohort ($n=469$) did not find any association between baseline IGA or EASI and risk of DROSD.[39] Therefore, the association between eczema severity and risk of DROSD remains uncertain.

A history of ocular disease prior to dupilumab treatment (predominantly self-reported) has been identified as a risk factor for DROSD.[18,39,40] In one report, estimation of the odds ratio (OR) has reflected a strong association with a history of any eye disease (OR 2.97, 95% CI 1.76–5.01) and prior use of an ophthalmic medication (OR 5.16, 95% CI 3.11–8.58).[39]

Few prospective studies included detailed ophthalmological assessment prior to treatment.[41,42] In one study, 46 individuals with moderate-to-severe AD identified for initiation of dupilumab were consecutively sampled for a study with examination by an ophthalmologist (i) prior to commencing dupilumab and (ii) at week 16; 16 patients developed DROSD (35%). All cases with pre-existing dry eye disease ($n=20$) were advised to apply ocular lubricants. In this group, 45% developed DROSD, whereas in the group without pre-existing dry eye disease, 30% developed DROSD. When dry eye disease was classified into those with and without keratitis, the risk of DROSD was associated only with pre-existing dry eye disease *and* keratitis (OR 6.3, CI 1.3–31.6). Additionally, the presence of eyelid eczema increased the risk of DROSD (OR 8.7, CI 1.8–40.6). Interestingly, DROSD was not associated with a history of allergic conjunctivitis.[41]

A further, recent, prospective, French multicentre study of 181 adult patients with AD who underwent ophthalmologist assessment at baseline and week 16 showed that of 34 cases who developed DROSD, 32 had no pre-existing blepharoconjunctivitis, yet 50% had reported prior dry eye disease. Indeed, 25 of 27 with baseline blepharoconjunctivitis showed no change or improvement in their ocular surface disease.[42] Small case series also point to the possibility of dupilumab benefiting some forms of ocular surface disease including vernal keratoconjunctivitis ($n=3$).[43]

The risk of DROSD appears to be lower in younger age groups. It has been reported in young children (0.5–6 years, $n=197$, DROSD 5% vs. 0% placebo), children (6–11 years, $n=362$, DROSD 7.2% vs. 4.2% placebo) and adolescents (12–16 years, $n=251$, DROSD 10.3% vs. 4.7% placebo).[44–46] Although this appears to be a lower prevalence than that identified in adults, to date most paediatric data are derived from randomized controlled trials. Importantly, the increased risk in adolescents is similar to that noted initially in randomized controlled trial data in the adult population, and the strongest DROSD signal in adults came from postmarketing surveillance and observational cohorts. However, a single-site observational dataset ($n=89$, mean age 12.6, SD 2.9) reported 7% with conjunctivitis or blepharitis, which supports clinical trial data in real-world cohorts.[47] Within the adult population, patient age was not associated with risk of DROSD,[39] which mirrors clinical trial data,[18] but in an older group the rates of DROSD may be lower. In an observational study of patients aged > 65 years ($n=105$), DROSD was identified in only 13.3%.[48]

There is little evidence to support the use of blood parameters to predict risk of DROSD. In an industry-led, post hoc analysis of all adolescent and adult patients in dupilumab clinical trials ($n=5612$), data were not differentiated between AD ($n=2629$) and asthma and other atopic disorders ($n=2983$), despite the evidence that these disorders show different risks of DROSD.[18] In this report, higher baseline levels of IgE, eosinophils, and thymus and activation-regulated chemokine (TARC) were associated with increased risk of DROSD, but the results did not reach statistical significance.

A separate prospective, observational study showed that baseline elevation of eosinophils (> 350 vs. ≤ 350 cells μL^{-1}; hazard ratio 3.99, 95% CI 1.71–9.29) and IgE (> 3637 vs. ≤ 100 kUA L^{-1}; hazard ratio 3.15, 95% CI 1.2–8.26) correlated with an increased risk of DROSD.[49] A further study did not support the association with baseline eosinophil counts but did show that individuals with higher increases in eosinophil counts during therapy were at increased risk of DROSD.[39] A retrospective review of the baseline characteristics of 57 adult patients with DROSD showed significantly higher levels of IgE and TARC ($P<0.01$), but not eosinophils or disease severity, in association with DROSD.[50]

Recommendations

1. Prevention in adults and children

a. Can we reduce the risk of DROSD?

Prophylactic use of ocular lubricants alongside dupilumab treatment may reduce the risk of DROSD in patients with AD. In a prospective study from Italy of 30 patients with

severe AD, none had developed ocular symptoms or objective evidence of conjunctivitis or keratitis at 6 months while using concurrent artificial tears.[51] The concomitant prescription of preservative-free lubricating eye ointment prior to dupilumab was reported in two other retrospective studies from Italy of 104 and 277 patients, and 1.9% and 7.2% developed DROSD, respectively.[52,53] However, in a study from London of 100 cases, DROSD was identified in 76% of cases despite prescription of preservative-free lubricating eye ointment with dupilumab.[23] It is difficult to reconcile these differences and it should be noted that two real-world observational datasets from Italy, where no prophylactic lubricant usage was recorded, duly showed high levels of DROSD (40%, $n=72$; and 15.2%, $n=289$),[49,54] suggesting that the differences seen from the London study are not due to low background levels of DROSD in Italy.

To investigate the effect or prevalence of pre-existing eye disease, a retrospective study examined a series of 43 patients with AD treated with dupilumab where ophthalmologist preassessment was introduced. Baseline ophthalmology assessment identified an abnormal ocular surface in 61% of these patients. In affected individuals, prior to commencing dupilumab, patients were started on eye treatment as indicated: warm compress (58%), artificial tears (25%) and antihistamine drops (8%). The incidence of DROSD reduced from (28%, 5 of 18) to (12%, 3 of 25) following the introduction of ophthalmology assessment at baseline.[55] In another prospective study of 25 patients, baseline ophthalmology assessment identified ocular surface alterations in all patients at baseline (grade 1–3 erythema) and this did not correlate with the patient-reported measures of disease severity (OSDI score).[56]

Overall, there is weak evidence to support the prophylactic use of lubricants. While it would be ideal to direct treatment towards any pre-existing eye disease through routine baseline assessments conducted by an ophthalmologist for all patients starting dupilumab, this is not a feasible expectation. However, in those individuals with pre-existing ocular surface disease, there is evidence that intervention with simple treatment may reduce the risk of DROSD.[56] The consensus of the DOCWG was that it would be beneficial for individuals commencing dupilumab therapy to be given standard advice about eye care to prevent ocular surface disease, such as limiting screen time and avoiding environments that have ocular irritants (e.g. smoke, pollution and cooling fans).

2. When should initiation of dupilumab therapy be delayed for ophthalmological assessment?

In most cases, dupilumab therapy should proceed based on joint decision making between the dermatologist and patient and not be delayed for ophthalmology input. However, pre-existing eye disease should be assessed by the dermatologist before prescribing (Figure 1a). A history of severe corneal or conjunctival eye disease such as corneal transplant or keratoconus should indicate a need for discussion with ophthalmology prior to initiation of dupilumab, where cases can be risk stratified as to their need for prior ophthalmological assessment or any prophylactic measures to be introduced.

While a history of nonsevere conjunctival or corneal disease should not delay commencement of dupilumab therapy, it would warrant coadministration of lubricants, and referral to ophthalmology should be initiated only if symptoms worsen. Routine referral should be reserved for cases with significant pretreatment chronic eye disease. Therefore, ongoing mild or moderate chronic eye disease such as atopic keratoconjunctivitis should not delay initiation of dupilumab, but coadministration of lubricants is recommended, and referral to ophthalmology if symptoms worsen. New, acute symptoms of ocular inflammation, such as those suggesting infective conjunctivitis, should be treated as per routine management, and it is recommended that dupilumab therapy is commenced once the symptoms have resolved (Table 9).

3. Making the diagnosis including adults and children

a. Ocular disorders: which eye problems are associated with dupilumab?

Following a systematic search of the literature, a list of potential diagnoses associated with DROSD was compiled

Table 9 Ocular history and effect on dupilumab initiation

Ocular symptoms, signs and diagnosis	Action (all ages)
Current	
Recent onset of new symptoms (usually allergic or infective)	Treat and delay dupilumab initiation until resolved
Keratoconus	Delay dupilumab initiation until ophthalmology advice, may need prior assessment
Chronic symptoms of ocular surface inflammation	*Mild to moderate* Initiate dupilumab and ocular lubricant *Significant or severe* Delay dupilumab initiation until ophthalmology advice
Past history	
Corneal transplant, keratoconus	Delay dupilumab initiation until ophthalmology advice, may need prior assessment
Atopic (kerato)conjunctivitis, blepharitis or recurrent infection	Do not delay dupilumab initiation, no need to refer to ophthalmology, initiate ocular lubricant therapy
Past history of ocular herpes simplex virus (HSV)	
Other chronic ocular surface problems, previously managed by ophthalmology	Do not delay dupilumab initiation, no need to refer to ophthalmology, initiate ocular lubricant therapy
Past history of facial (nonocular) HSV	Do not delay dupilumab initiation, no need to refer to ophthalmology

(Table 8). To determine the incidence of individual ocular diagnoses in cases of DROSD, it is necessary for ophthalmologists to examine all cases in any reported clinical study. Limited data were available with confirmed ophthalmological review of all cases, but they suggest that multiple ocular diagnoses can frequently be identified in the same individual with DROSD. However, the majority of diagnoses are conjunctivitis, blepharitis, dry eye and keratitis (Table 10). A recent analysis of the World Health Organization's VigiBase for adverse drug reactions associated with the use of dupilumab supported these findings.[57] There were no reports of an ocular surface disease unique to dupilumab. Therefore, diagnosis should be undertaken as per routine practice in ophthalmology.

b. What should dermatologists do to monitor for DROSD?

The primary symptoms of DROSD are bilateral red eye, ocular irritation and/or pain, and hazy vision. Dermatologists should check individuals prescribed with dupilumab for symptoms of ocular inflammation, and any individuals reporting eye symptoms should be assessed to determine whether the diagnosis is likely to be DROSD. In brief, this should include an assessment of the history of the problem focusing on onset and duration, change in vision, severity of pain, foreign body sensation, discharge, itch and photophobia. Importantly, unilateral symptoms are unlikely to represent DROSD and should prompt urgent management pathways. Examination of the eyes by dermatologists should include routine assessment and documentation, including the presence or absence of redness. If it is present, an assessment of corneal surface ulceration, haze, opacity or purulent discharge should be made. When necessary, loss of visual acuity should be assessed by asking patients to read with one eye covered, reporting any reduction in vision.

Individuals on less frequent face-to-face follow-up programmes should be encouraged to attend their optometrist on an annual basis for an ocular checkup. Dermatologists should be aware that cicatricial change is not always symptomatic and, therefore, noninflammatory ocular symptoms should prompt optometrist or ophthalmologist review.

For all patients aged < 7 years, any symptom warrants early ophthalmology advice because younger patients tolerate a high level of ocular surface inflammation and, therefore, any presentation of ocular symptoms is potentially severe.

Table 10 Ophthalmologist-reported diagnoses in cases of atopic dermatitis treated with dupilumab

Ophthalmologist diagnosis	Incidence (all)[a]	Frequency (DROSD)[b]
Conjunctivitis	13%	49%
Dry eye	13%	36%
Keratitis	11%	38%
Blepharitis	8%	29%

[a]Incidence in all treated cases. [b]Frequency within cases of dupilumab-related ocular surface disorders (DROSD); multiple ophthalmological diagnoses in individual cases are possible.[24,39,41,73,76,103,104]

i. Urgent (within 24 h) ophthalmological referral

Referral for same-day assessment by ophthalmology or to eye casualty is recommended when a dupilumab-treated patient presents with redness of the conjunctiva plus any of the red flag symptoms or signs: worsening visual acuity (self-assessed), ocular pain, sensitivity to light or visible damage to the cornea (Table 4).[58] Unilateral eye symptoms are very unlikely to be dupilumab related and should be managed through existing pathways.[1,2] If possible, local pathways may facilitate telemedicine review by ophthalmology, which may provide an effective way for urgent initial ophthalmology advice.

ii. Nonurgent ophthalmology referral

In cases of DROSD that do not fulfil the RAPID criteria (Table 4), standard referral pathways should be followed if appropriate,[1,2,59] or specific pathways for DROSD as described here. There is no clinical trial evidence addressing initial management by dermatologists. However, it was the view of the DOCWG that such cases should be classified as mild, moderate or severe based on the symptoms and degree of conjunctival and limbal redness (Figure 2). In nonurgent, mild-to-moderate cases of DROSD in patients aged ≥ 7 years, treatment should be initiated by dermatology and reviewed before referral. In moderate-to-severe cases, treatment should be initiated, and for those who do not respond to treatment a 'soon' (i.e. < 4 weeks) referral to ophthalmology arranged (Figure 1b). For children aged < 7 years with eye signs or symptoms, severity should be jointly assessed in conjunction with ophthalmology advice (remote or face to face).

In general, mild-to-moderate DROSD includes intermittent symptoms such as foreign body sensation or eye rubbing, or mild and intermittent conjunctival injection or eyelid swelling. For mild-to-moderate DROSD in children aged < 7 years, ocular lubricants should be commenced, and an ophthalmology referral arranged for review within 4 weeks of onset of the eye symptoms. For children aged < 7 years with severe DROSD, lubricant treatment can be commenced; however, ophthalmology review should be conducted within 1 week. Patients awaiting routine ophthalmology outpatient appointments should be encouraged to report any change in the severity of their symptoms. While assessment by an optometrist would be helpful in monitoring the ocular surface, the view of the DOCWG was that management of DROSD would be outside the remit of an optometry practice. Therefore, routine assessment by optometrists is not recommended.

c. What should ophthalmologists do to assess DROSD?

The diagnosis of DROSD is simply any ocular surface disease in a patient on dupilumab. As discussed above, the conditions may exist prior to dupilumab therapy and may have worsened or be *de novo* in that individual. To date, there have been no reports of any unique ocular pathology induced by dupilumab. Therefore, routine ophthalmological history and examination are recommended, as for the underlying ocular surface disease. Various screening tools

have been validated that may offer a useful means for ophthalmologists to characterize DROSD in detail. For example, conjunctivitis can be assessed with the activity and damage index score;[60] dry eye with the Ocular Staining Score or Oxford Grading Scale,[61,62] and MGD with the MGD score.[63] Age-specific disease severity measures should be considered as appropriate, for example adolescent-specific tools.[64]

However, there is no evidence that these scores improve patient care in DROSD, and therefore, the consensus of the DOCWG was that they should not be recommended routinely in patient assessment. Instead, many such scores will be employed most widely in an observational registry or clinical trial setting, to better assess DROSD while it is still a new condition. The consensus of the DOCWG was that ophthalmology review also offers an important opportunity to screen for keratoconus, which may otherwise remain undiagnosed.

4. Treatment

a. How should DROSD be treated by the dermatologist?

The published literature reports a variety of different treatment approaches (Table 11). No data from randomized clinical trials were available to assess treatment effectiveness, but reported outcome data where clinical response to interventions was reported are summarized in Table 12. These showed good evidence for the benefit of tacrolimus ointment, and topical corticosteroid eyedrops (89% and 74% of cases showed good or very good response, respectively). Ocular lubricants, ciclosporin eyedrops and lid hygiene measures were less effective (65%, 63% and 50% of cases achieved a good or very good response, respectively). Antihistamine therapy was the least effective of the therapies where outcome data could be compared (42% good or very good response). It is expected that treatment initiated for DROSD in secondary care would be continued in primary care as per the guidance here.

Dermatologists should assess DROSD as described above and summarized in Figure 1b. In paediatric cases (< 7 years), early discussion (< 7 days) with ophthalmology is indicated before treatment is commenced.

Table 11 Treatment approaches in dupilumab-related ocular surface disorders

Treatment class	Formulation or active ingredient
Lubricants or artificial tears	Formulations not always specified, mostly containing hyaluronic acid
Antihistamine eyedrops	Olopatadine Epinastine Bepotastine 1.5% Ketotifen
Calcineurin inhibitor	Tacrolimus 0.03%, 0.1%; ocular and lid skin Pimecrolimus 1.0% lid skin cream Ciclosporin 0.5%, 1.0% (ointment) and 0.2%, 0.1% (drops)
Corticosteroid eyedrops	Prednisolone Fluorometholone Dexamethasone Betamethasone Difluprednate Lotepredno l Hydrocortisone
Allergen avoidance	Patch-test dependent
Antibiotic drops	Moxifloxacin 0.5% Azithromycin 1% Chloramphenicol Levofloxacin
Antifungal agent	Ketoconazole 2% Itraconazole 200 mg (orally, twice daily)
Anti-inflammatory	Azathioprine Lifitegrast 1%, 5%[a]
Antiviral agent	Aciclovir (varicella zoster meningitis)
Warm compress	Mechanical warming

[a]Unlicensed in the UK (adapted from Foley *et al.*).[105]

i. Lubricants

Ocular lubricants (Table 2) are very well tolerated and cost-effective for dry eye conditions.[20,41,52,53,55,65–83] When recommending ocular lubricants, it is important to also provide general advice about lifestyle measures that are important in this condition.[1] Recommended ocular lubricants include preservative-free hyaluronates drops. Typically, one drop should be applied to each eye applied twice to four times daily; for children aged < 7 years, lubricants should only be recommended following discussion with ophthalmology. Formulations with higher hyaluronate percentage are considered to offer greater therapeutic efficacy, and therefore should be used in more severe disease.

To date, there is no clear evidence that pre-emptive treatment with ocular lubricants reduces the risk of DROSD (see above). In those with pre-existing eye disease (defined as those individuals who had previously been managed in ophthalmology for a chronic ocular surface disease) ocular lubricants should be coprescribed with dupilumab.

In those who develop mild or moderate DROSD, ocular lubricants have been shown to be beneficial. Response to lubricant therapy should be assessed at 4 weeks by the patient or dermatology team, as appropriate; if it is ineffective, then treatment should be escalated through the pathway.

ii. Antihistamine eyedrops

Although the evidence base for benefit from antihistamine therapy is very limited, the view of the DOCWG was that this would be a reasonable mode of therapy to try in mild-to-moderate cases.[25,41,55,65–67,69,71,75,77–79,84,85] Therefore, if lubricants are not effective, or the ocular inflammation is classified as moderate, then olopatadine eyedrops may be trialled, twice daily, in addition to the ocular lubricants. Treatment should be assessed at 1 month; lack of response to treatment warrants routine ophthalmology referral. The experience of the DOCWG is that antihistamine eyedrops are unlikely to be beneficial for children aged < 7 years with DROSD and this should not delay referral to ophthalmology.

iii. Anti-inflammatory treatment with tacrolimus ointment

Most cases of DROSD are very responsive to anti-inflammatory treatment. However, topical corticosteroids should only be initiated following ophthalmology assessment. In those aged > 17 years presenting with severe symptoms, while

Table 12 Reported treatment outcomes from observational series of dupilumab-related ocular surface disorders (DROSD)

Treatment	No. reported	No. included	Responders	References
Tacrolimus ointment	53	38	89%	20, 25, 53, 66–68, 70, 72, 73, 76, 78, 80, 86, 87
Corticosteroid eyedrops	218	172	74%	20, 25, 41, 52, 53, 55, 65–71, 74–88, 106–109
Lubricants	542	57	65%	20, 41, 52, 53, 55, 65–83
Ciclosporin eyedrops	44	40	63%	41, 53, 55, 66, 67, 69, 71, 75, 76, 78, 79, 81–83, 85–88
Lid hygiene measures	15	10	50%	55, 74, 76, 77, 79, 81
Antihistamines	61	24	42%	25, 41, 55, 65–67, 69, 71, 75, 77–79, 84, 85

The absolute number of cases of DROSD reported to have been treated with a specific treatment (no. reported) is greater than the number of cases where outcomes from treatment were recorded (no. included). Responder percentages were calculated from the meta-analysis of reported 'good' or 'very good' responses.

awaiting ophthalmology review, it was the consensus of the DOCWG that a trial treatment with tacrolimus 0.1% ointment, applied once daily to the external eyelids and including the lid margins for 2–4 weeks, should be undertaken in appropriate patients (typically those who have tolerated tacrolimus ointment in the past, or in those who have not had tacrolimus ointment).[20,25,53,66–68,70,72,73,76,78,80,86,87] It should be explained specifically that the ointment can be applied directly to the ocular surface of the lids (off licence) for best effect, but this would typically be initiated by ophthalmology. In cases treated with tacrolimus ointment, ophthalmology review should be arranged within 4 weeks. However, these cases should not have their referral delayed so as to assess response. This approach is not recommended in those with a history of ocular-surface herpes simplex virus or varicella zoster virus.

Tacrolimus ointment can be considered in those aged 2–17 years; however, it should be used only following advice from ophthalmology. The view of the DOCWG was to commence with tacrolimus 0.03% ointment; however, increasing the potency to tacrolimus 0.1% ointment would be acceptable as an off-licence treatment in appropriate cases.

iv. Topical ciclosporin eyedrops

Ciclosporin eyedrops are licensed for use in severe keratitis in dry eye disease that has not responded to treatment with tear substitutes. As such, the application of this treatment to DROSD has been reported.[41,53,55,66,67,69,71,75,76,78,79,81–83,85–88] It was the consensus of the DOCWG that although topical ciclosporin eyedrops should usually be initiated by ophthalmologists, they may be suitable for dermatologists to initiate under agreed local pathways.

v. Other interventions

On a case-by-case basis, other options can also be considered by dermatologists. These include lid hygiene measures.[55,74,76,77,79,81] For asymptomatic patients and those with blepharitis or lid margin disease, the evaporative component of dry eye can be managed by encouraging healthy tears to lubricate the eyes, prevent premature evaporation of the tears and reduce inflammation. This can be promoted by application of warm compresses to the closed eye, but this approach is generally only feasible in adults; for detailed prescribing see the BAD guideline for managing people with rosacea.[89] This approach can be trialled for up to 3 months but should be discontinued if eye symptoms worsen.

Because of the potential for scalding, a flannel soaked in hot water is not recommended, and instead, specially designed, battery-powered devices or microwaveable eyelid warming devices should be used, followed by eyelid massage to soften the oils, and cleaning eyelid margins to unblock the oil glands and remove excess bacteria. Homemade bicarbonate solution, or commercially available lid wipes can be used for this purpose. This approach is not recommended in children, because the aetiology of the DROSD is highly unlikely to adhere to the warm-compresses regimen.

One small, retrospective study reported a significant improvement in ocular surface disease in four of nine patients following the identification and subsequent avoidance of contact allergic allergens.[90] However, in this study eyelid eczema was included under the definition of ocular surface disease, which makes it unclear whether the eyelid eczema improved or whether ocular surface disease responded. Patch testing patients with AD on dupilumab with persistent facial and eyelid eczema has been suggested previously,[90] but the role of patch testing in the management of DROSD is unclear.

Previous reports have demonstrated that dupilumab dose reduction can maintain good disease control in people with AD[91–93] and may be expected to reduce the risk and severity of ocular adverse events. In a small study of 15 patients with DROSD, increased dose intervals to 300 mg 3-weekly led to an improvement in DROSD symptoms in 47% of cases.[94] Therefore, dose reduction may be a useful approach in selected patients, especially those with good skin control. However, further research is needed in this area.

b. How should DROSD be treated by the ophthalmologist?

Assessment of inflammatory ocular surface disease is routine for ophthalmologists and DROSD does not warrant a specific approach, but recognition of the association between dupilumab and ocular surface disease is required. See Table 7 for standard approaches to assessment.

The principle for ophthalmology treatment should be guided by the assessment as directed by the ophthalmological diagnosis at assessment. Bacterial or viral infections should be treated appropriately.

i. Mild disease

Treatment should be age specific. Even mild disease should be treated by ophthalmology in those aged < 7 years because

of the limited ability to communicate symptomatology, and risk of interference with normal ocular development before this age. All patients with DROSD should be offered treatment with lid hygiene and ocular lubricants (Table 2). Preservative-free formulations are recommended because of the increased incidence of allergic contact dermatitis in the treatment group. Antihistamine drops can also be added to regimens for mild-to-moderate DROSD (Table 5), and warm compresses may be beneficial in cases of MGD.

ii. Moderate-to-severe disease (differences in children)

Most cases of moderate-to-severe DROSD and refractory cases of mild DROSD will likely be considered appropriate for short-term treatment with topical corticosteroids, typically preservative-free dexamethasone 0.1%. It was the consensus of the DOCWG that 8 weeks would be a sensible maximum for short-term treatment with topical corticosteroids. Prolonged treatment requires careful consideration of the risk–benefit profile and should warrant a joint discussion with dermatology to consider changing dupilumab treatment. It was the consensus of the DOCWG that corticosteroid-sparing agents should be started early to facilitate the tapering of ocular corticosteroids as soon as possible. Typically, this would involve long-term maintenance with tacrolimus ointment or ciclosporin drops.

iii. Treatment-resistant disease

For treatment-resistant disease, it is important to consider the option of changing dupilumab therapy to an alternative. However, combination treatment with topical corticosteroids, tacrolimus ointment and ciclosporin drops has been utilized by some members of the DOCWG with success, although the evidence base is lacking; therefore, such an approach should be used only in carefully considered cases. Therapy with autologous or allogeneic serum eyedrops may be considered in line with guidance on its use in cases refractory to conventional and licensed treatments.

Serum eyedrops contain many factors that are present in tears, providing a nutritional tear film substitute with biological properties that promote ocular surface renewal and immunological defence and restore tear film homeostasis. Serum eyedrops may be produced from a patient's own blood (autologous) or from healthy volunteer donors (allogeneic). Serum eyedrops can only be initiated at specialized centres commissioned to deliver this service.[95,96]

c. What eye problems should prompt dupilumab withdrawal?

Generally, treatment withdrawal has been infrequently required and has been said to be necessary in only 0.5% of cases.[19] However, with the increasing availability of highly effective novel therapies with a significantly reduced risk of ocular surface disorders, the appropriateness of these treatments for patients with DROSD should contribute to the decision making when switching treatment is required. Limited data exist for switching dupilumab to Janus kinase inhibitors. In one report, three patients with DROSD were switched to abrocitinib, and by 12 weeks two showed resolution of their eye symptoms.[97] This emphasizes the importance of good communication between the patient, the dermatologist and the ophthalmologist. Patients established on dupilumab therapy should be assessed on a case-by-case basis for treatment benefit vs. risk, and if alternative treatments are available. Dupilumab is recommended to be withdrawn in the following circumstances:

- Progressive loss of visual acuity that is unresponsive to treatment (assessed by ophthalmology).
- People with progressive conjunctival cicatrization (scarring) are likely to require dupilumab withdrawal but should be assessed on a case-by-case basis.

The following eye problems should prompt a discussion with dermatology and ophthalmology and the patient, about alternative treatment options to dupilumab therapy:

- Significant risk that visual acuity may be reduced because DROSD inflammation (e.g. progressive conjunctival cicatrization) is not responding to treatment (inadequately controlled).
- Significant risk of serious ocular adverse effects from requirement for prolonged ocular topical corticosteroid therapy (> 8 weeks).
- Significant loss of quality of life for the patient caused by inadequately controlled DROSD, for example as measured by DLQI, Children's DLQI or OSDI.

Discussion

DROSD is a range of different ocular surface disorders that have long been recognized by ophthalmologists, and to date there appears to be no evidence that dupilumab induces a unique ocular surface disorder. Although it has been demonstrated that dupilumab is detectable in tear fluid and at higher concentrations in more severe DROSD, the precise pathogenic cause for DROSD and why it should manifest with multiple ocular surface presentations remain to be fully determined.[98] DROSD is a relatively common complication of dupilumab therapy for treatment of AD and arises in approximately 25% of treated individuals in the first 4 months of treatment, less commonly in children. Although rates of DROSD appear lower in children, which is in line with their lower likelihood of past ocular surface disease, this may also be because currently, there are far fewer observational data available for children.

The most important risk factor for development of DROSD appears to be a history of ocular surface disease, and such patients should be offered prophylactic treatment with lubricants at the outset of dupilumab therapy, even though the evidence base for this intervention is lacking. For those with pre-existing, severe corneal or conjunctival eye disease, such as a history of corneal transplant or keratoconus, it is recommended that initiation of dupilumab is delayed at least until there has been discussion with ophthalmology to consider the risks and plan further management.

In most cases, the symptoms of DROSD comprise mild irritation and redness, which settle with simple intervention, such as ocular lubricants, and can often be managed effectively by dermatologists. However, some patients will develop severe or chronic disease. In such cases, close

liaison with ophthalmology is essential and important in children, especially those aged < 7 years. Mostly, treatment ladders parallel those employed routinely by ophthalmology, but certain disorder-specific approaches are important, such as application of tacrolimus ointment to the lid margins.

Treatment with topical corticosteroids is usually highly effective for DROSD, and in most cases, after short term treatment, it can be gradually withdrawn as symptoms improve. For this reason, the consensus of the DOCWG was that, for those cases where topical corticosteroid drops are required for > 6 weeks, introduction of corticosteroid-sparing therapy should be recommended despite the lack of an evidence base for this. For those with persistent DROSD and dependency on ocular corticosteroid therapy, a significant risk of adverse effects exists, and the option of changing to an alternative systemic therapy needs to be considered in such cases.

While the introduction of dupilumab for treatment of AD has revolutionized the management of moderate-to-severe AD, it is important to note that since the licensing of dupilumab, many other highly effective therapies such as Janus kinase inhibitors have been licensed for treatment of AD, some of which may carry other risks, but do not carry the same risk of ocular adverse effects. However, it is increasingly clear that other biologics targeting the IL-13 pathway, such as tralokinumab[99] and lebrikizumab,[100] show an increased risk of ocular surface disease.

In the absence of head-to-head comparative studies between dupilumab, tralokinumab and lebrikizumab in matched patient populations, it is difficult to draw conclusions as to the relative risk with each therapy. Indirect comparisons suggest a lower incidence with tralokinumab compared with dupilumab and lebrikizumab, which appear to have broadly similar risks. The summaries of product characteristics for all three therapies include ocular surface disorders as adverse effects. It seems likely that most of the guidance reported here will be appropriate for management of ocular surface disease associated with these other therapies targeting the IL-13 pathway; however, this will be subject to further assessment as the evidence permits. Based on current evidence, monoclonal antibodies targeting type 2 pathways other than IL-4/IL-13, including IL-31, do not have this pattern of ocular adverse effects.

In conclusion, close working between ophthalmology and dermatology is required to offer the patient the best advice on the risk, if any, from chronic DROSD or its treatment with continued dupilumab therapy vs. the possibility of changing treatment.

Recommended audit points

Dermatology

Audit of screening for and detection of previous ocular surface disorders

Review of the last 50 consecutive people with AD commencing dupilumab therapy (no more recently than the last 18 months) to contain relevant screening information for predisposition and during initial care:

- Is there an explicit account of the absence/presence of previous inflammatory disorders of the ocular surface or lid margins?
- If present and history positive, has the patient been seen by an ophthalmologist in the past for this?
- Is it documented that the patient was provided with an information leaflet on dupilumab that includes information and guidance on ocular adverse effects?
- At all follow-up appointments, within the first year after dupilumab initiation, are there explicit questions and answers documented concerning ocular surface problems?

Audit of managing ocular surface disorders once detected

In a sample of 20 consecutive people with AD with previous inflammatory ocular or eyelid disorders, or those presenting with these disorders following commencement of dupilumab therapy, were:

- People with previous or current ocular surface disorders managed in ophthalmology offered prophylactic ocular lubricants?
- People presenting with ocular surface disorders during dupilumab therapy documented as having presence/absence of red flag features (Table 4)?
- People presenting with ocular surface disorders during dupilumab therapy documented as having their ocular disorders graded as mild/moderate/severe (Figure 2)?
- People presenting with ocular surface disorders during dupilumab therapy documented as having been prescribed ocular lubricants plus one topical antihistamine or/and topical tacrolimus?
- People presenting with ocular surface disorders during dupilumab therapy documented as having their treatment outcomes assessed at 4 weeks (± 1 week)?
- People presenting with ocular surface disorders during dupilumab therapy documented as having any redness of the conjunctiva with any red flag signs or symptoms, and seen by ophthalmology within 24 h of features being documented in dermatology?

Ophthalmology

In the last 20 consecutive people with AD who developed DROSD, is there clear documentation of:

- Time between referral and ophthalmology assessment?
- Assessment of disease severity, for example with a symptom score (OSDI), staining score (OSS/Oxford) or tear film breakup time?
- Change in visual acuity?
- Exclusion and treatment of presumed infection in those with severe cases?
- Monitoring for corticosteroid eyedrop adverse events, for example intraocular pressure and retinal nerve fibre layer optical coherence tomography (note: not for active herpetic disease)?

Stakeholder involvement and peer review

The draft expert consensus paper was peer reviewed initially by the BAD's Therapy & Guidelines subcommittee and the Royal College of Ophthalmologists' Bowman Club, then made available to the BAD and Royal College of Ophthalmologists memberships, and Sanofi. The comments received were considered actively by the authors; the finalized version was signed off by the respective organizations' aforementioned subcommittee and club prior to submission for publication.

Limitations

This document has been prepared on behalf of the BAD and the Royal College of Ophthalmologists and is based on the best data available when the document was prepared, as well as expert clinical consensus among dermatologists and ophthalmologists. Where evidence-based data were not available, recommendations were based primarily on expert consensus, and were labelled as a Good Practice Point (GPP). While the group agreed that the management approach reported here is likely to apply to all ocular complications associated with IL-13 pathway inhibition in AD, the limited depth of data beyond dupilumab prevented us from making specific recommendations about the other drugs. It is important to recognize that this limitation in the published data requires clinicians to apply these guidelines in a patient-centred manner and we recognize that under certain circumstances it may be necessary to deviate from the recommendations. Failure to adhere to these recommendations should not necessarily be considered as negligence, nor should adherence to these recommendations constitute a defence against a claim of negligence.

Plans for revisions

In view of rapid progress in the licensing of biologic therapies for AD, as well as acquisition of safety and side-effect data from ongoing clinical trials, patient registries and postmarketing surveillance, we acknowledge that these recommendations will require early review. This is planned for 2025.

Acknowledgements

The authors would like to thank everyone who contributed to this expert consensus guidance article, including the patient representative Alice Payne, and the wider BAD and Royal College of Ophthalmologists memberships.

Funding sources

Development of this expert consensus paper has been funded independently by the British Association of Dermatologists (BAD) and the Royal College of Ophthalmologists. Clinicians' salaries are funded by their National Health Service or university affiliations; no additional remunerations are involved in relation to this project.

Conflicts of interest

MRA-J: speaker, adviser, honoraria, travel/research/departmental grants, from the Biotechnology and Biological Sciences Research Council, British Skin Foundation, UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918), AbbVie, Almirall, Amgen, Ducentis, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi, UCB and Unilever. **SJB**: speaker honoraria (British Society for Paediatric Dermatology), research grants (Wellcome Trust, British Skin Foundation, European Lead Factory, BIOMAP Consortium, Pfizer Sosei Heptares). **CF**: chief investigator for the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (NCT03270566) trials, UK-Irish Atopic eczema Systemic Therapy Register (A-STAR), principal investigator BIOMAP Consortium, lead EU Trans-Foods consortium, departmental funding (Sanofi Genzyme, Pfizer), compensation from the *British Journal of Dermatology* and EuroGuiDerm (guidelines lead), speaker fees (Almirall, Bioderma, Sanofi). **PH**: speaker fees (Santen, Thea Pharmaceuticals), clinical trials principal investigator (Sifi Pharmaceuticals, Syneos Pharma, Novartis), research grants (Royal College of Surgeons, Edinburgh). **ADI**: consultancy honoraria (AbbVie, Arena Pharmaceuticals, Aslan, BenevolentAI, Chugai, Connect Biopharma, Dermavant, Genentech, LEO Pharma, Lilly, Menlo Therapeutics, Novartis, Pfizer, Regeneron, Sanofi, UCB). **GAJ**: honorarium (Sanofi). **SML**: coinvestigator BIOMAP Consortium, research grants from Wellcome Trust. **PL**: honoraria and/or grants (AbbVie, Janssen, LEO Pharma, Eli Lilly, Sanofi, Novartis). **DO'D**: speaker honoraria (AbbVie, Pfizer). **DO'K**: speaker and adviser honoraria (Sanofi, AbbVie, Novartis, Janssen). **GP**: honoraria and/or grants (Sanofi, Amryt, Krystal Biotech, Incyte). **AEP**: investigator, speaker, adviser or research/educational support (AbbVie, Pfizer, Eli Lilly, LEO Pharma, Galderma, Almirall, Boehringer Ingelheim, UCB, Bristol Myers Squibb, Amgen, Novartis, Janssen). **S Rauz**: research grants from the Medical Research Council (MRC), National Institute for Health and Care Research (NIHR), Sight Research UK, and Fight for Sight. **S Robbie**: honorarium (LEO Pharma), adviser (Sanofi). **SKG**: grant (Sanofi). **MS**: travel grants or conference fees (LEO Pharma, UCB). **RTW**: investigator, speaker, adviser or educational support (AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galderma, LEO Pharma, Janssen, Novartis, Pfizer, Sanofi, UCB), honoraria and consultancy (National Institute for Health and Care Excellence, clinical expert). The remaining authors declare no conflicts of interest.

Data availability

No data were generated.

Ethics statement

Not applicable.

Patient consent

Not applicable.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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