

Management of dupilumab-associated ocular surface diseases in atopic dermatitis patients

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Summary

Atopic dermatitis is a chronic inflammatory skin disease characterised by eczematous skin lesions and intense pruritus. It is often associated with other atopic diseases such as allergic rhinitis and conjunctivitis, bronchial asthma and eosinophilic oesophagitis. Dupilumab is the first biologic approved for the treatment of moderate-to-severe atopic dermatitis in Switzerland. Dupilumab targets the interleukin (IL)-4/IL-13 receptor and thus inhibits the signalling of IL-4 and IL-13, two key mediators of type 2 inflammation, resulting in an improvement of clinical signs and symptoms of atopic dermatitis. Patients with atopic dermatitis present more often with ocular surface diseases (OSDs), such as allergic conjunctivitis, blepharitis and keratitis as well as infectious conjunctivitis and keratoconus compared with the general population. Upon dupilumab therapy, increased rates of ocular surface diseases have been reported in clinical trials. Interestingly, dupilumab-associated (da) OSD is restricted to atopic dermatitis patients and has not been observed in asthma and chronic rhinosinusitis trials. Fortunately, most cases of dupilumab-associated OSD are mild-to-moderate and transient. Thus, ocular surface disease presents a particular adverse event of treatment with dupilumab in dermatology. This article aims at providing a practical guide for physicians, with a special focus on dermatologists, allergists and ophthalmologists in Switzerland, to the diagnosis and management of dupilumab-associated OSD in atopic dermatitis patients.

For this purpose, an expert group of dermatologists and ophthalmologists from university and cantonal hospitals in Switzerland reviewed data on ocular surface diseases published in clinical trial and real-life reports of dupilumab therapy, published case reports and case series on the management of dupilumab-associated OSD, as well as recent recommendations provided by experts of national and international boards. Based on the observations of

dupilumab-associated OSD and practical experiences in identifying and treating OSD, an algorithm has been developed that is specific to the needs in Switzerland. Considering concomitant ocular diseases and differential diagnoses, the clinical presentation of dupilumab-associated OSD and its response to therapeutic measures, a step-wise approach is recommended. Mild dupilumab-associated OSD can be managed by dermatologists and allergists, whereas patients with moderate-to-severe OSD requiring corticosteroid or calcineurin inhibitor therapy should necessarily be referred to an ophthalmologist. The effects of preventive measures, such as artificial tears, are uncertain. The recommendations provided here should guarantee a prompt and effective treatment of OSD for patients under dupilumab therapy in order to prevent that an otherwise potent therapy has to be ceased because of ocular adverse events.

Introduction

A Swiss expert group of dermatologists and ophthalmologists with experience in the treatment of ocular surface diseases (OSDs) in patients with atopic dermatitis from university and cantonal hospitals reviewed data in clinical trials and real-life reports on dupilumab therapy, published case reports on the management of OSD, as well as recent national and international recommendations. Based on the observations of dupilumab-associated OSD and practical experience in identifying and treating OSDs, an algorithm has been developed that is specific to the needs in Switzer-

ABBREVIATIONS

EASI	Eczema Area and Severity Index
IGA	Investigator Global Assessment
IL	interleukin
OSD	ocular surface disease
SCORAD	scoring atopic dermatitis

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land. The level of agreement in the development of the algorithm was determined with the consent of seven of the nine experts.

Atopic dermatitis: epidemiology and clinical characteristics

Atopic dermatitis is a chronic inflammatory skin disease presenting with recurrent eczematous lesions, intense pruritus and increased risk of skin infections [1, 2]. It affects approximately 20% of all children up to the age of 6 years and 5% of adults in Western industrialised countries [1]. Because of its chronic disease course, it requires long-term treatment [1]. Atopic dermatitis is based on a genetic predisposition, which affects both the epithelial barrier and a type 2 based immune reaction [3].

Besides affecting the skin, atopic dermatitis is associated with substantial psychosocial distress as well as with other atopic diseases such as bronchial asthma, allergic rhinitis and eosinophilic oesophagitis [4–6].

Ocular surface diseases frequently associated with atopic dermatitis

Patients with atopic dermatitis have an increased risk of different ocular surface diseases with conjunctivitis as the most frequent ocular comorbidity in the atopic dermatitis population (supplementary table S1 in the appendix) [7, 8].

Incidence and differential diagnosis of ocular surface diseases in atopic dermatitis

Ocular surface diseases, such as allergic conjunctivitis, blepharitis and keratitis, are well-known ophthalmic comorbidities in patients with atopic dermatitis, in particular those with severe disease in whom incidence rates of 32.4–55.8% have been reported [9]. For atopic keratoconjunctivitis alone in atopic dermatitis patients, an incidence rate of 25% to 42% is given [10].

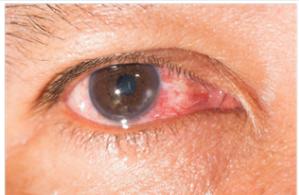
Since the clinical signs and symptoms of allergic conjunctivitis are not pathognomonic, it is essential to consider a broad spectrum of differential diagnoses (fig.1). As trigger of OSD, in particular when associated with lid dermatitis, irritant and allergic contact dermatitis have to be ruled out [11].

Red flags for immediate ophthalmological consultation are loss of transparency in the eye, vision loss, discharge and an increase in ocular pressure [12]. Patients wearing contact lenses presenting with red eyes should immediately be referred since they are at high risk of having an infectious keratitis.

Mode of action of dupilumab

Dupilumab, a monoclonal antibody, targets the shared interleukin (IL)-4/IL-13 receptor α -chain and thus blocks the action of IL-13 and IL-4 (fig. 2) [1, 13]. IL-13 in particular has been shown to play a key role in the pathogenesis of atopic dermatitis [1].

Figure 1: Common ocular surface diseases in atopic dermatitis patients. Stock pictures by istock and shutterstock.

	<p>Conjunctivitis (inflammation of the conjunctiva)</p> <p>Conjunctivitis may be acute (red eye) or chronic (pink eye). The redness affects the entire conjunctiva, including the inner sides of the eyelids (bulbar and tarsal conjunctiva). The diagnosis of conjunctivitis is based on the aspect of ocular discharge (serous, purulent or mucopurulent), and on careful examination of the tarsal conjunctiva. An eversion of the upper eyelid is necessary to detect the presence of papillae or follicles. Infections, allergy and physicochemical irritation are the most common causes. Symptoms are a feeling of pressure or foreign body sensation, burning and itching, but no pain. Itching is a typical symptom of allergic and atopic conjunctivitis.</p>
	<p>Keratitis (inflammation of the cornea)</p> <p>Keratitis is always associated with intense pain. Further symptoms include foreign body sensation and photophobia. Typical findings are redness of the eye, a watery or purulent secretion and impaired visual acuity (due to loss of corneal transparency). Flashlight examination may reveal large corneal ulcers or opacification, but fluorescein staining and slit-lamp examination is necessary to detect smaller lesions.</p>
	<p>Blepharitis (inflammation of the eyelid)</p> <p>Blepharitis corresponds to inflammation of the eyelid margin. Blepharitis is classified as either anterior, with crusty eyelids and sticky eyelashes (typical of staphylococcal and seborrheic blepharitis), or posterior due to Meibomian gland dysfunction (chalazion, which consists of an obstruction of a Meibomian gland or oily secretions). Symptoms are a sandy feeling that can be associated with photophobia and/or increased tear flow.</p>
	<p>Dry eye</p> <p>Dry eye is due to insufficient tear secretion or excessive evaporation. Symptoms are scratchy and foreign body sensations. The conjunctiva appears normal but can be hyperaemic in the palpebral fissure. Paradoxically, a sensation of increased tear flow may occur. Keratoconjunctivitis sicca in severe dry eye syndrome (mainly in Sjögren's syndrome) is characterised by the presence of filamentous keratitis (filaments consisting of adherent complexes of mucus and epithelium). Fluorescein staining is useful for its detection. A feeling of dryness can occur despite normal tear production, for example, in the case of abnormal tear fluid composition, excessive evaporation, or irritation by exogenous triggers.</p>

Efficacy and safety of dupilumab

In several clinical trials in patients with moderate-to-severe atopic dermatitis, dupilumab has been shown to exhibit an excellent and well-balanced efficacy and safety profile [14–19]. A 75% improvement of the Eczema Area and Severity Index (EASI) was achieved in 47.7% to 69% of dupilumab-treated patients versus 13.3% to 29.6% of the placebo group after 16 weeks [15, 16, 20]. More detailed information is provided in table S1, in the appendix) [14–19]. The most common adverse events observed were injection site reactions (9.6%), conjunctivitis (>1%, <10%), blepharitis (>1%, <10%) and oral herpes (>1%, <10%) [21].

Dupilumab-associated OSD exclusively affects atopic dermatitis patients

Results from clinical trials

In clinical trials, the diagnosis of conjunctivitis was usually reported by dermatologists and allergists, whereas no specific assessments by ophthalmologists were required for diagnosis. Therefore, a specific categorisation of conjunctivitis is not available and the frequencies reported include all cases of conjunctivitis regardless of their aetiology. The incidence of conjunctivitis was 17.9–22.1% in the dupilumab and 7.9–11.1% in the placebo group after 16 weeks (table S1). Numerical differences between placebo

and dupilumab were apparent after about 4–8 weeks [9, 14–19].

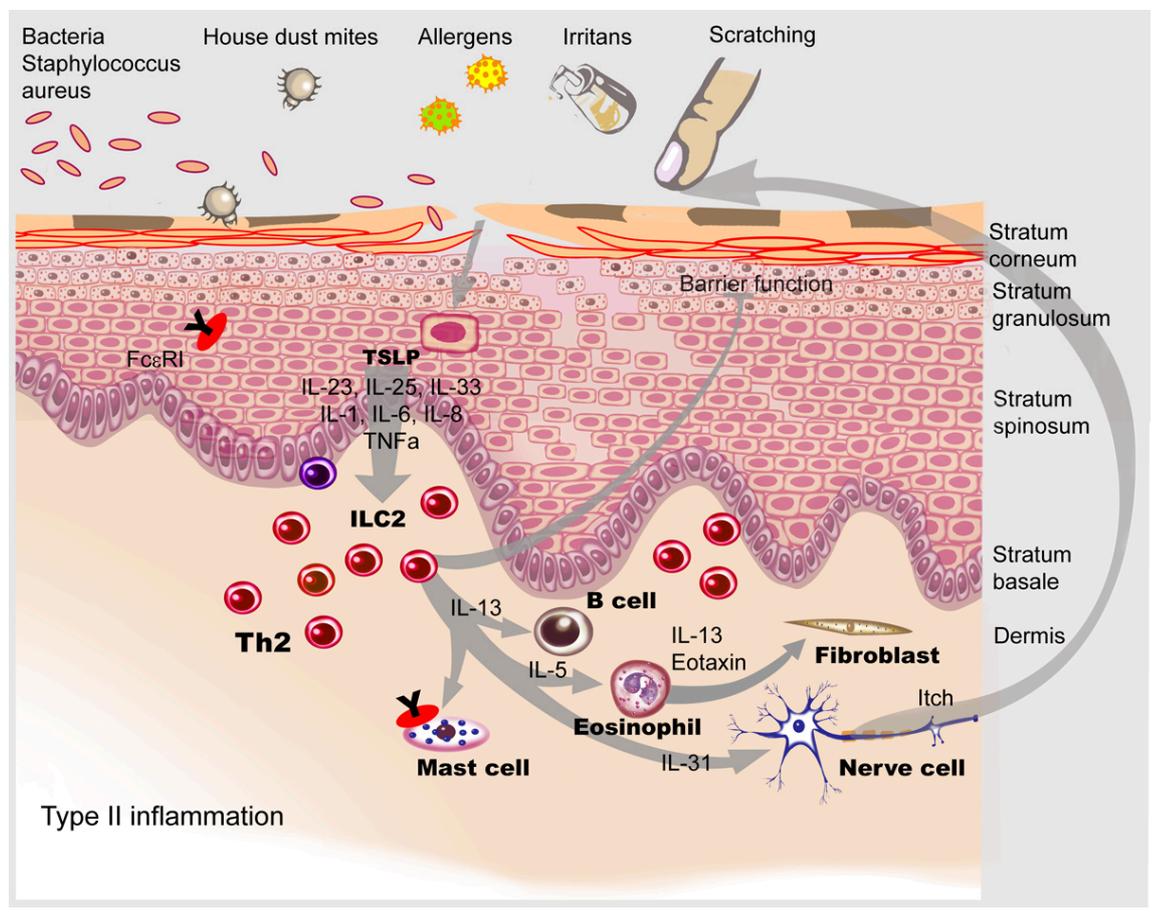
In a long-term open-label extension study for patients previously enrolled in phase II and III studies, conjunctivitis was reported in only 10.7%, suggesting that it mainly occurs during the first months of dupilumab therapy and may recover [18]. In most cases, conjunctivitis was mild to moderate [18]. Overall, there were <1% of patients who discontinued dupilumab treatment because of ocular adverse events [9]. Moreover, in a long-term study, the incidence rates of 4.7% and 4.9%, respectively, were similar in both dupilumab and placebo groups at week 36, indicating that dupilumab-associated OSD is transient [9, 14–16].

Higher baseline severity of atopic dermatitis and levels of thymus and activation-regulated chemokine (TARC), total immunoglobulin E and blood eosinophil counts, as well as a history of conjunctivitis were associated with an increased risk to develop a dupilumab-associated OSD [9]. Still, the pathogenesis of dupilumab-associated OSD and the reason why it occurs almost exclusively in atopic dermatitis patients needs to be elucidated.

OSD in clinical trials with dupilumab in other diseases

In atopic diseases other than atopic dermatitis, such as asthma, chronic rhinosinusitis with nasal polyposis or eosinophilic oesophagitis, dupilumab therapy was not associated with an increased risk for conjunctivitis, suggesting that the relatively high rates of conjunctivitis in atopic

Figure 2: The targets of dupilumab in atopic dermatitis skin characterised by a type 2 immune reaction. Illustration: Aldona von Guten (modified from: Simon D, Wollenberg A, Renz H, Simon HU. Atopic Dermatitis: Collegium Internationale Allergologicum (CIA) Update 2019. Int Arch Allergy Immunol. 2019;178(3):207–18 [1], reprinted with permission from S. Karger AG, Basel).



dermatitis trials may reflect unique effects of dupilumab on the ocular surface of these patients [9, 16, 22–25].

Observations in clinical practice

So far, real-world evidence data on the efficacy and safety of dupilumab in atopic dermatitis patients from the Netherlands, France and Denmark are available [26–28]. Here, conjunctivitis rates of 18.4%, 34.1% and 38.2%, respectively, have been reported (supplementary figure S1 in the appendix) [26–28]. Moreover, both severity of atopic dermatitis and the age of the patients were associated with dupilumab-associated OSD [8]. It appears that dupilumab-associated OSD in real-world evidence with unselected patients probably having more comorbidities, occurs more frequently than in clinical trials [26].

Hypotheses on the pathogenic mechanisms in dupilumab-associated OSD

Various hypotheses have been proposed for mechanisms that drive conjunctivitis in atopic dermatitis patients treated with dupilumab. These include inflammatory and non-infectious processes such as unmasking preexisting sub-clinical atopic or allergic inflammatory processes [8], quantitative and qualitative tear production failures [8], the IL-4 mediated lipogenesis by Demodex mite colonisation of the Meibomian glands, an increased systemic bioavailability of free IL-4 and IL-13 causing inflammatory symptoms, a decrease of IL-13 mediated mucus production and an IL-13-related scarcity of conjunctival goblet cells [8, 29, 30].

Management of dupilumab-associated OSD in atopic dermatitis patients

Based on the literature and our own experiences we developed recommendations on how to manage dupilumab-associated OSD (fig. 3):

- Depending on the clinical presentation of dupilumab-associated OSD and its response to therapeutic measures, a *stepwise approach* is recommended.
- *Before initiating dupilumab treatment*: If a patient presents with ocular disorders that cannot be managed by a dermatologist or allergist, an ophthalmological examination should be planned to diagnose preexisting eye disease.
- Due to the lack of clinical experience and study data, recommendations for prophylactic treatment cannot be provided.
- *Step 1: measures taken by dermatologists and allergists*: If clinical signs and symptoms of dupilumab-associated OSD such as hyperaemia, tearing, dry eye, sand corn feeling and pruritus appear, warm compresses and artificial tears and ointments can be used as first line.
- If a seasonal or perennial allergic conjunctivitis is present, topical or systemic antihistamines are recommended.
- Single dose units should always be preferred to prevent adverse events (irritation or allergic reaction) caused by preservatives.

- If symptoms are not relieved within one to two weeks, the topical application of calcineurin inhibitors on the eyelids or diclofenac eye drops can be considered. Physicians should be aware that these substances may cause burning and irritation, respectively, in dry eye.
- *Red flags for an urgent ophthalmologic consultation are*: vision loss, pain, purulent discharge, corneal involvement and conjunctival scarring [12]. Patients wearing contact lenses should rapidly be referred in the presence of ocular symptoms [31].
- *Step 2: measures taken by ophthalmologists*: If clinical signs and symptoms of OSD do not respond to the therapeutic measures described in Step 1 within 1 to 2 weeks, the patient has to be referred to an ophthalmologist. As topical corticosteroids can cause increased intraocular pressure in 20% of patients even after only 2 weeks, intraocular pressure has to be measured prior to and during use of steroids. Topical corticosteroids with low penetration rate into the eye such as fluorometholone should be preferred.
- If OSD does not improve despite topical corticosteroids within 2 to 3 weeks, topical ciclosporin (ciclosporin 1 mg/ml eye drops), emulsion or lifitegrast, an antagonist of the integrin lymphocyte function-associated antigen 1/LFA-1 (lifitegrast 50 mg/ml eye drops) should be considered. Of note, for reimbursement of ciclosporin and lifitegrast eye drops, an application for cost assumption by the patient's health insurance company may be required.

Outlook

In the spectrum of OSD, dupilumab-associated OSD presents a novel subgroup that poses a challenge for all, dermatologists, allergists and ophthalmologists. Specific challenges are

1. For the dermatologist and allergist:

- (a) to diagnose dupilumab-associated OSD and distinguish it from other OSDs
- (b) to evaluate the severity of OSD
- (c) to manage mild forms of dupilumab-associated OSD
- (d) to interact with ophthalmologists
- (e) to be aware of red flags on severe forms requiring urgent ophthalmological intervention

2. For the ophthalmologist:

- (a) To recognise dupilumab-associated OSD as a novel adverse effect of atopic dermatitis therapy
- (b) To interact with dermatologists
- (c) To manage severe forms of dupilumab-associated OSD requiring immunosuppressive or immunomodulating therapy

As result of our expert group meeting, we provide a summary of current knowledge on dupilumab-associated OSD and its management in daily practice. The discussion on and our clinical experience with dupilumab-associated OSD clearly demonstrate how important the collaboration between dermatologists, allergists and ophthalmologists is in order to achieve best therapeutic results for atopic dermatitis patients. We are aware that, as we will learn more

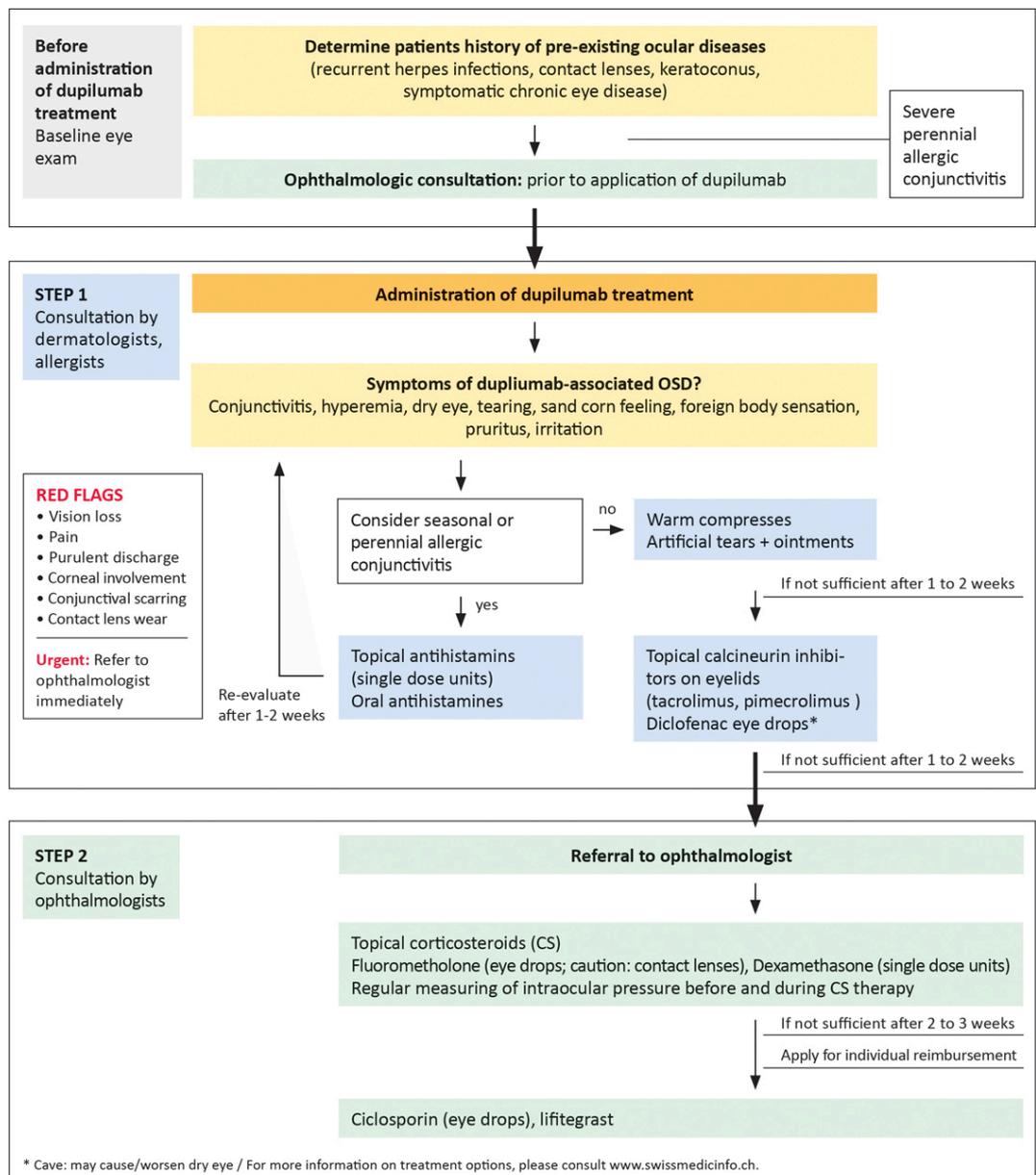
on the pathogenesis of dupilumab-associated OSD, on how to identify patients at risk and therapeutic approaches, we will probably have to adapt and revise our recommendations in the near future.

Approval for dupilumab in Switzerland

Indication: Dupilumab (Duxipent®) was approved in Switzerland in April 2019 and is indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients and adolescents aged 12 years and older when treatment with prescription topical medications does not provide adequate disease control or is not recommended. Duxipent can be used with or without topical corticosteroids [21].

Administration: Duxipent® (dupilumab) is administered in an initial dose of 600 mg by subcutaneous injection (two injections of 300 mg each), followed by a dose of 300 mg by subcutaneous injection every 2 weeks for the treatment of adult patients (from the age of 18) with severe atopic dermatitis (Investigator Global Assessment [IGA] 4, on an IGA scale of 0–4, or scoring atopic dermatitis (SCORAD) score >50 or EASI ≥21.1), if patients have had an inadequate response to intensified local treatment with prescription topical therapies (topical corticoids and/or calcineurin inhibitors) and phototherapy (if available and indicated) and systemic treatment with a conventional immunosuppressive agent (excluding systemic corticoids) for at least 1 month, or where these therapies are contraindicated or have had to be discontinued because of clinically relevant adverse events. Duxipent® is not reimbursed in

Figure 3: Algorithm for the management of dupilumab-associated ocular surface diseases in atopic dermatitis patients developed by a Swiss expert group of dermatologists and ophthalmologists.



combination with other systemic drugs for the treatment of atopic dermatitis. If after 16 weeks of treatment with Duxipent® no therapeutic success has been achieved, i.e., an IGA reduction of ≥ 2 points compared with the initial value or a $\geq 50\%$ improvement of the EASI score compared with the initial value or a $\geq 50\%$ improvement of the SCORAD score compared with the initial value, treatment must be discontinued. The treatment costs are reimbursed after prior consultation with a medical examiner. The diagnosis, prescription of Duxipent® and follow-up may only be made by a specialist in dermatology and venereology or a specialist in allergology and clinical immunology. After 52 weeks of uninterrupted therapy, the health insurer must again approve the costs after prior consultation with the medical advisor [25].

Financial disclosure

The contents of this practice guide were developed by Swiss experts in the therapy of atopic dermatitis and eye diseases on the occasion of an expert meeting. The expert meeting was supported by Sanofi Genzyme.

Potential conflicts of interest

Y. Guex-Crosier: none; J. Di Lucca has served as investigator for Roche Pharma and Eli Lilly, and advisor for Sanofi Genzyme; P. Häusermann has served as a speaker, and/or advisor for AbbVie, Almirall, Amgen, Celgene, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Sanofi Genzyme; E. Laffitte has served as an investigator, speaker, and/or advisor from AbbVie, Amgen, Celgene, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Merck Sharp & Dohme, Sanofi Genzyme and Pfizer; L. Saulite: none; P. Schmid-Grendelmeier has received honoraria for advisory boards and as speaker from AbbVie, LEO Pharma, GlaxoSmithKline, Novartis, Pfizer, Roche Pharma and Sanofi Genzyme; K. Schürch: none; K. Thormann: none; D. Simon reports serving as an investigator and/or consultant for AbbVie, Astra Zeneca, Galderma, Eli Lilly, Pfizer, Roche Pharma and Sanofi Genzyme.

The authors have no conflicts of interest that are directly relevant to the content of this article.

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Appendix: Supplementary data

Table S1:

Efficacy and safety of dupilumab in phase III clinical trials [14–19]. (Disclaimer: The only approved dosing regimen of dupilumab for the treatment of moderate-to-severe atopic dermatitis is every 2 weeks.)

SOLO 1, 16 weeks [14]			Dupilumab 300 mg, q2w (N = 224)	Placebo (N = 224)		
	Efficacy	EASI 75	115 (51%)	33 (15%)		
		IGA Score 0 or 1	85 (38%)	23 (10%)		
	Safety, dupilumab 300 mg, q2w	AEs: injection-site reaction (8%), exacerbation of AD (13%), headache (9%), allergic conjunctivitis (5%), nasopharyngitis (10%), upper respiratory tract infection (3%), conjunctivitis (5%), any herpes viral infection (7%), adjudicated skin infection (6%), non-skin infection (30%)	AEs (≥1), 166 (73%)	AEs (≥1), 144 (65%)		
	OSD	Conjunctivitis	11 (5%)	2 (1%)		
		Conjunctivitis allergic	12 (5%)	2 (1%)		
SOLO 2, 16 weeks [14]			Dupilumab 300 mg, q2w (N = 233)	Placebo (N = 236)		
	Efficacy	EASI 75	103 (44%)	28 (12%)		
		IGA Score 0 or 1	84 (36%)	20 (8%)		
	Safety, dupilumab 300 mg, q2w	AEs: injection-site reactions (14%), exacerbation of AD (14%), headache (8%), allergic conjunctivitis (1%), nasopharyngitis (20%), upper respiratory tract infection (3%), conjunctivitis (4%), any herpes viral infection (4%), adjudicated skin infection (6%), non-skin infection (25%)	AEs (≥1), 154 (65%)	AEs (≥1), 168 (72%)		
	OSD	Conjunctivitis	9 (4%)	1 (< 1%)		
		Conjunctivitis allergic	2 (1%)	2 (1%)		
LIBERTY AD CHRONOS, 16 weeks, 52 weeks [15]			Dupilumab 300 mg, q2w + TCS (N = 106), week 16	Placebo, qw + TCS (N = 315), week 16	Dupilumab 300 mg, q2w + TCS (N = 89), week 52	Placebo, qw + TCS (N = 264), week 52
	Efficacy	EASI 75	73 (69%)	73 (23%)	58 (65%)	57 (22%)
		IGA Score 0 or 1	41 (39%)	39 (12%)	32 (36%)	33 (13%)
	Safety, dupilumab 300 mg, q2w + TCS, 52 week-pe- riod	AEs: nasopharyngitis (23%), upper respiratory tract infection (10%), sinusitis (2%), influenza (4%), eye disorders (31%), conjunctivitis (14%), atopic dermatitis (18%), injection site reaction (15%), asthma (5%), headache (5%), non-herpetic skin infections (11%), any herpes infections (7%)			AEs ≥1 97 (88%)	AEs ≥1 266 (84%)
	OSD, 52 week-period	Conjunctivitis (conjunctivitis allergic, conjunctivitis bacterial, atopic keratoconjunctivitis, and conjunctivitis)	15 (14%)	25 (8%)		
LIBERTY AD CAFÉ, 16 weeks [16]			Dupilumab 300 mg, q2w + TCS (N = 107)	Placebo + TCS (N = 108)		
	Efficacy	EASI 75	67 (62.6%)	32 (29.6%)		
		IGA	43 (40.2%)	15 (13.9%)		
	Safety, dupilumab 300 mg, q2w + TCS	AEs: nasopharyngitis (20.6%), conjunctivitis (11.2%), oral herpes (2.8%), gastroenteritis (1.9%), upper respiratory tract infection (0.9%), pharyngitis (0.9%), herpes simplex (0.9%), atopic dermatitis (7.5%), allergic conjunctivitis (15%), lacrimation increased (0.9%), fatigue (3.7%), injection site reaction (0.9%), injection site erythema (0.9%), headache (9.3%), rhinitis allergic (6.5%), cough (3.7%), oropharyngeal pain (2.8%), asthma (0.9%), diarrhea (2.8%), back pain (0.9%), vascular disorders (3.7%), hypertension (0.9%), blood and lymphatic system disorders 3.7%, lymphadenopathy (1.9%), skin infections, excl. herpetic infections (1.9%)			AEs ≥1, 77 (72%)	AEs ≥1, 75 (69.4%)
	OSD: Treat- ment-emer- gent con- junctivitis	Conjunctivitis			12 (11.2%)	3 (2.8%)
		Conjunctivitis allergic			16 (15%)	7 (6.5%)
		Adenovirus conjunctivitis			1 (0.9%)	0.00%
		Conjunctivitis bacterial			1 (0.9%)	2 (1.9%)
		Conjunctivitis viral			1 (0.9%)	1 (0.9%)
SOLO-CONTINUE, 36 weeks [17]			Dupilumab 300 mg, q8w (N = 84)	Dupilumab 300 mg, q4w (N = 86)	Dupilumab 300 mg, qw or q2w (N = 169)	Placebo (N = 83)
No./Tot No.(%)	Efficacy	EASI 75	45/82 (54.9%)	49/84 (58.3%)	116/162 (71.6%)	24/79 (30.4%)
No./Tot No.(%)		IGA score 0 or 1	21/64 (32.8%)	29/66 (43.9%)	68/126 (54%)	9/63 (14.3%)
	Safety, dupilumab	AEs: dermatitis atopic (20.4%), nasopharyngitis (19.2%), upper respiratory tract infection (7.8%), headache (4.8%), herpes simplex virus infection (4.2%), asthma (2.4%), back pain (3.6%), oral herpes infection (1.8%), influenza (2.4%), bronchitis (1.8%), urticaria (3.0%), arthralgia (3.0%),	AEs ≥1, 63 (75%)	AEs ≥1, 64 (73.6%)	AEs ≥1, 118 (70.7%)	AEs ≥1, 67 (81.7%)

SOLO 1, 16 weeks [14]			Dupilumab 300 mg, q2w (N = 224)	Placebo (N = 224)
300 mg, wk or q2w	pharyngitis (1.8%), diarrhea (2.4%), pruritus (1.8%), sinusitis (3.6%), blood creatin phosphokinase increased (0.6%), cough (2.4%), insomnia (2.4%), nasal congestion (2.4%), contact dermatitis (0.6%), gastroenteritis (1.8%), ligament sprain (1.2%), toothache (2.4%), contusion (0.6%), hypertension (1.2%), proteinuria (0.6%), rhinitis (0.6%), tonsillitis (0.6%), urinary tract infection (1.2%), viral infection (1.2%), ophthalmic herpes infection (0.6%), musculoskeletal pain (0.6%), vulvovaginal candidiasis (1.2%), fall (0.6%), eye disorders with preferred term conjunctivitis (5.4%), non-herpetic skin infections (2.4%), injection-site reaction (10.8%)			
OSD	Conjunctivitis: conjunctivitis, conjunctivitis bacterial, conjunctivitis viral, conjunctivitis allergic, and atopic keratoconjunctivitis		3 (3.6%)	4 (4.6%)
OPEN LABEL EXTENSION, week 52 [8], 76 [18] and week 148 [19]			Dupilumab 300 mg, qw (N = 428), week 52	Dupilumab 300 mg, qw (N = 284), week 76
n/sub-group (%)	Efficacy	EASI 75	346/398 (86.9%)	220/249 (88.4%)
n/sub-group (%)		IGA score 0 or 1	221/398 (55.5%)	144/249 (57.8%)
Safety, 76 week-period	AEs: nasopharyngitis (20%), upper respiratory tract infection (9.5%), dermatitis atopic (8.2%), headache 7.1%), oral herpes (4.3%), blood creatin phosphokinase increased (3.6%), bronchitis (3.2%), diarrhea (2.7%), back pain (2.7%), viral upper respiratory tract infection (2.5%), cough (2.3%), influenza (2.1%), conjunctivitis (10.7%), injection site reaction (10.1%)			AEs ≥1, 1054 (70.7%)
				AEs ≥1, 2264 (84.6%)

Figure S1: Real world evidence data of dupilumab collected in country-specific registries [26–28].

	The Netherlands ²⁵		France ²⁶		Denmark ²⁷	
	Baseline	Week 16	Baseline	Month 3	Baseline	Month 3
N	138	136	241	136	38	30
EASI score	median (IQR)		median +/- IQR		median (min-max)	
	19.9 (13.6-28.3)	4.0 (2.0-7.6)	17.9 +/-15.4	4.0 (2.0-7.6)	24.5 (6.4–71.4)	4.1 (0–19.7)
EASI change from baseline	mean (SD)		median percent change +/- IQR		median (SD)	
	-	-16.3 (10.9)	-	-16.3 (10.9)	-	22.6 (15.4)
EASI-75, n (%)	-	82 (61.7)	-	82 (61.7)	-	19 (63.3)
DLQI score	median (IQR)		median +/- IQR		median (min-max)	
	12.5 (8.0-19.0)	3.0 (2.0-6.0)	13 (+/-11)	3.0 (2.0-6.0)	11.5 (2–21)	9 (0–22)
Conjunctivitis, n (%)	-	47 (34.1)	-	47 (34.1)	-	7 (18.4)
Other AEs (≥ 5%)	Eosinophilia, eye irritation, headache, injection site reaction, gastro-intestinal complaints		Ocular pruritus, blepharitis, xerophthalmia, keratitis, eosinophilis, injection-site reaction, herpes simplex virus infection of eye		-	