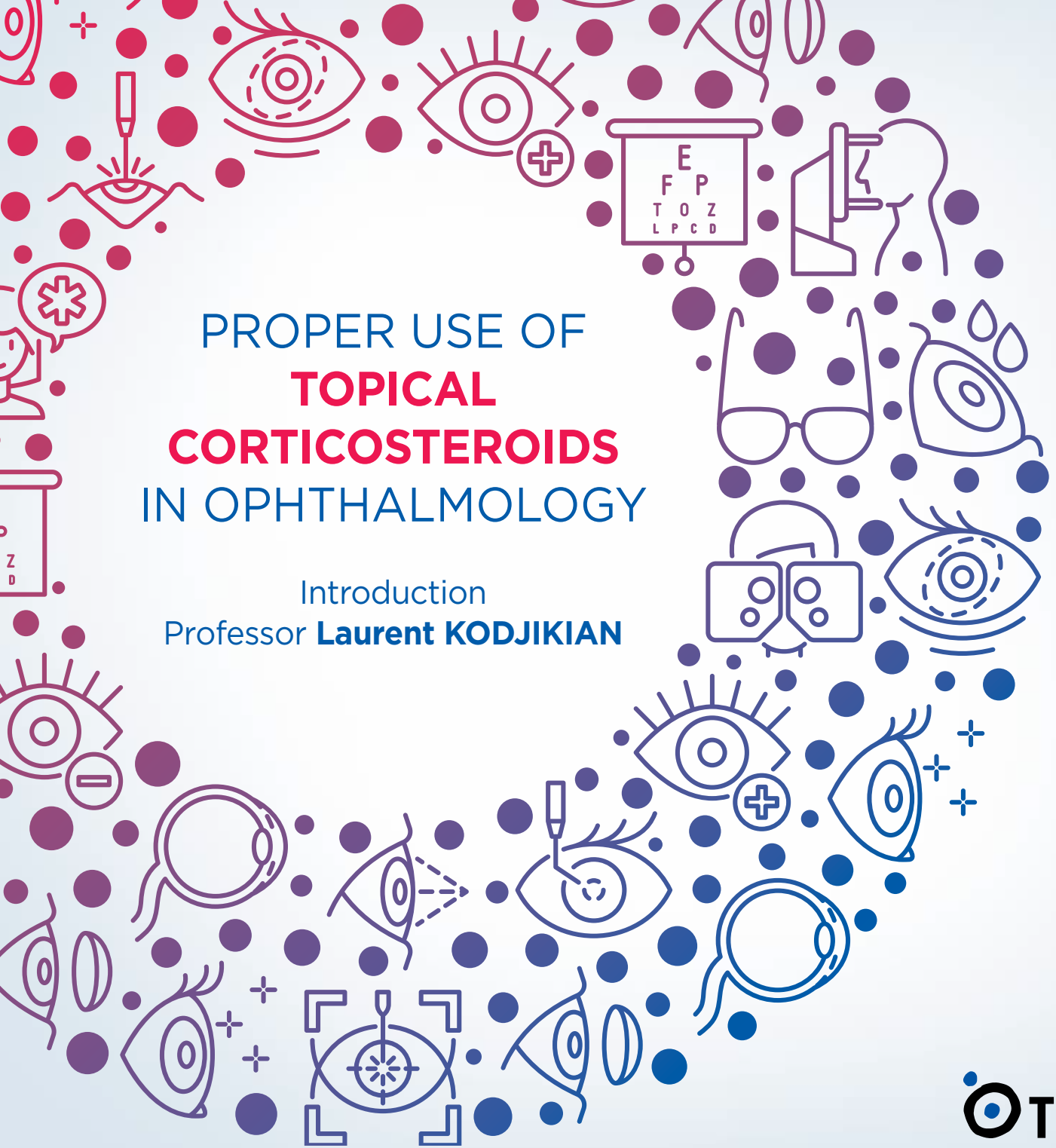

PROPER USE OF **TOPICAL CORTICOSTEROIDS** IN OPHTHALMOLOGY

Introduction

Professor **Laurent KODJIKIAN**

Théa

OVERVIEW

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INTRODUCTION

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The isolation of cortisol dates back to 1933 and its therapeutic use, initially in rheumatoid arthritis, began in the 1940s, leading to the Nobel Prize in Physiology or Medicine being awarded to Kendall, Reichsten and Henche for their work in 1950. As early as 1951, corticosteroids were used in ophthalmology and in acute uveitis. Since then, this therapeutic group has remained irreplaceable and widely prescribed.

Corticosteroid therapy has historically been part of the medical culture in France, where it is much more widely used than in the United States, with French physicians having a great deal of expertise in handling them and in managing side effects.

Corticosteroids used in ophthalmology can be administered through several possible routes, each with their respective advantages and disadvantages. They can also be used for multiple indications with variable levels of evidence, though they have always shown high efficacy in clinical practice.

Most of the indications for ophthalmic corticosteroid therapy have been known for a long time, but new indications are currently still emerging, such as for dry eye. Inflammation is a key mechanism in the pathophysiology of dry syndromes, which is now recognised worldwide thanks to the innovative work of Professor Christophe Baudouin and his team. Thus, short-term local corticosteroid therapy using a corticosteroid with a short half-life and low intraocular penetration may be effective in interrupting the vicious cycle of inflammation in dry eye with a low risk of side effects.

The side effects from ophthalmic corticosteroids, which frighten our American colleagues so much, can be prevented or controlled: the prescriber must be knowledgeable about them and carefully monitor treated patients, particularly in at-risk populations.

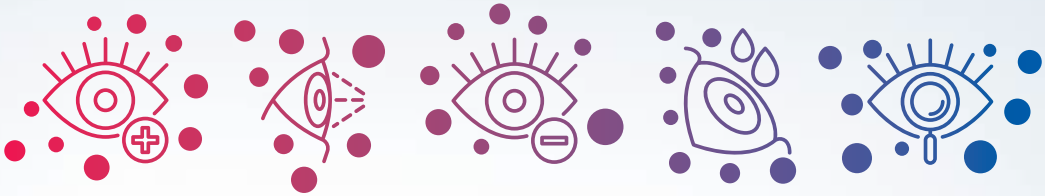
The purpose of this brochure is to review the various indications for topical corticosteroid therapy in ophthalmology, with its benefits, risks and precautions for use.

I would like to thank Laboratoires Théa for their historic commitment to providing educational support to ophthalmologists. Since the days of the “MSD Chibret Library”, many books and didactic brochures have been produced thanks to the enthusiasm of this internationally recognized French pharmaceutical company, which is unique enough to be emphasized.

I am proud to have the opportunity to provide the introduction to this new brochure, which supplements the previous ones, to provide an overview of corticosteroid therapy that will be useful to all ophthalmologists.

PART I:

CORTICOSTEROID USE IN OPHTHALMOLOGY



1 | MECHANISM OF ACTION OF CORTICOSTEROIDS

Natural corticosteroids synthesised by the adrenal glands either have a **predominantly** glucocorticoid **activity**, such as **cortisol**, or a predominantly **mineralocorticoid activity, such as aldosterone.**

Cortisol, also known as hydrocortisone, has glucocorticoid properties (particularly anti-inflammatory) and mineralocorticoid properties (anti-diuretic, anti-natriuretic and kaliuretic).

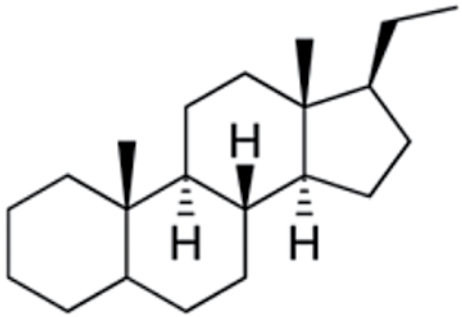
Hydrocortisone is used therapeutically, along with other hydrocortisone derived synthetic corticosteroids, to provide a longer **duration of action, greater anti-inflammatory activity and less mineralocorticoid** properties than the parent compound.

Glucocorticoids are classified in the steroidal anti-inflammatory therapeutic class.

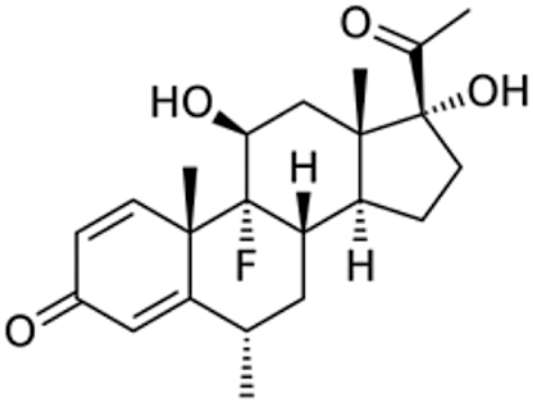
1.1 | MOLECULAR MECHANISM OF ACTION[1]

Glucocorticosteroids are structurally homogeneous with a pregnane core that carries functions essential to their biological activity, as well as functions that modulate this activity.

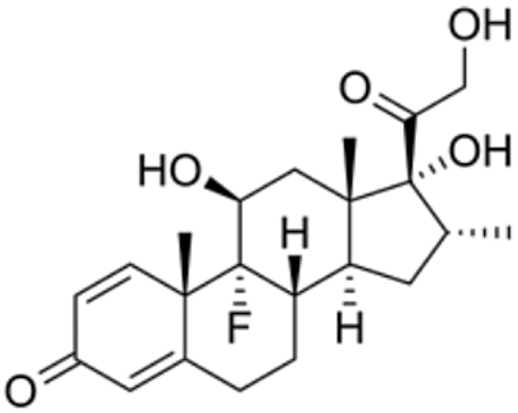
Glucocorticosteroids act through a specific receptor belonging to the nuclear receptor superfamily. This receptor, which is present in the inactive form of cytosol, is ubiquitous, as it is bound to a protein complex. Its density in cytosol is variable depending on the cell.



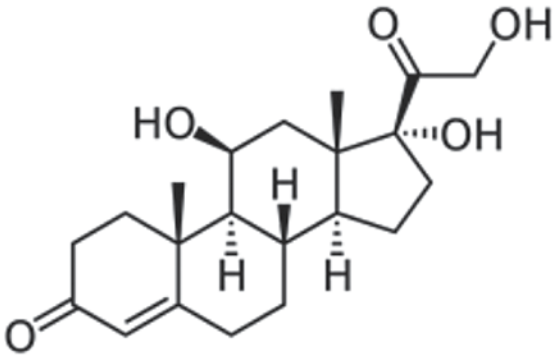
Pregnane core



Fluorometholone



Dexamethasone



Hydrocortisone

Only the free fraction of corticosteroid (i.e., 10 to 20%) is responsible for pharmacological activity via an intra-cytoplasmic receptor. The free molecule crosses the cell membrane using passive diffusion to bind with the receptor with a strong affinity. The binding of ligand to the receptor causes the protein complex to dissociate and the ligand-receptor assembly to migrate into the nucleus (nuclear translocation).

Glucocorticosteroids can regulate the expression of target genes through 3 distinct mechanisms of action:

- **Direct transcriptional action:** binding the glucocorticosteroid receptor to a nucleotide DNA sequence known as the Glucocorticosteroid Response Element (GRE), which exerts a transcription activation. This results in the increased production of anti-inflammatory proteins such as lipocortin-1 (or annexin-1), interleukin 10 or the IkB protein.

- **Indirect transcriptional action:** interaction between the glucocorticosteroid receptor and transcription factors NF-kappa B, NF-IL6, AP-1 and STATS, leading to the inhibition of these factors and thus to the repression of target genes. This interaction is the main mechanism responsible for the effects of glucocorticoids by controlling the expression of multiple inflammation genes as well as those of many cytokines (transcription activation or inhibition).

- **Action on the chromosomal structure:** modification of the chromatin structure, reducing the transcription factors' access to their binding sites and inhibiting the expression of the relevant genes.

Glucocorticosteroids could also exert non-genomic effects, which are responsible for their rapid effects, through membrane actions, post-transcriptional actions on mRNA, proteins.

1.2 | THE PHARMACODYNAMIC PROPERTIES OF CORTICOSTEROIDS[1,2]

Glucocorticosteroids are used to treat 3 effects: **anti-inflammatory, allergic and immunosuppressant.**

Corticosteroids exert an action on the various contributors in immunity and inflammation by inhibiting the transcription of pro-inflammatory cytokines and adhesion molecules. They inhibit the production of arachidonic acid via the synthesis of lipocortin-1, which has an anti-phospholipase A2 activity.

They induce a decrease in the differentiation and anti-infectious activity of macrophages, an inhibition of the function of suppressor and cytotoxic T-helper lymphocytes, and an inhibition of leukocyte influx at the inflammatory site by decreasing vascular permeability and activating endothelial cells.

Glucocorticosteroids also inhibit the IgE-dependent release of histamine and the release of leukotriene C4 through basophils and mast cell degranulation.

PHARMACOLOGICAL EFFECTS	MECHANISM OF ACTION	BIOLOGICAL CONSEQUENCES
ANTI-INFLAMMATORY EFFECTS	Inhibition of the production of pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNFalpha). Inhibition of the expression of cell adhesion molecules (ICAM). Inhibition of phospholipase A2 and type 2 cyclooxygenase. Inhibition of inducible NO synthase	Decreased influx of macrophages and granulocytes to the inflammatory site. Decreased transendothelial migration of phagocytic cells. Inhibition of the synthesis of pro-inflammatory eicosanoids (Prostaglandins, thromboxane, leukotrienes). Decreased production of radical species.
IMMUNOSUPPRESSANT EFFECTS	Decreased expression of MHC II molecules. Inhibition of IL-2 production.	Decreased protein antigenicity. Decreased lymphocyte proliferation, including: inhibition of the production, proliferation and the functions of Helper T-cells, suppressors and cytotoxic lymphocytes.
PRO-APOPTOTIC EFFECTS	Induction of cell death genes or the repression of factors or genes essential for cell life.	Cell death

Mechanisms of the effects of corticosteroids[1]

2 | COMPOUNDS AVAILABLE IN OPHTHALMOLOGY

Three compounds are available in France for topical use in ophthalmology[3]: **dexamethasone, fluorometholone and hydrocortisone.**

They can be used in ophthalmology through different local routes of administration[4]:

- Topical: eye drops as a solution or suspension, ointments, whose viscosity allows for prolonged contact with the ocular surface and penetration.
- Periocular injections in the form of injectable preparations that could be “delayed”.
- Intravitreal injections.

Finally, systemic corticosteroids may be indicated in certain ophthalmological conditions.

Corticosteroids can be classified according to their anti-inflammatory potency and half-life. The anti-inflammatory potency has been conventionally set at 1 for the hydrocortisone reference compound and is expressed as a multiple of this reference potency for the other compounds.

INN (anti-inflammatory potency from 1 to 25)	TRADE NAME	ASSOCIATED ANTIBIOTICS	FORMS/ PRESERVATIVES
HYDROCORTISONE/1	Softacort® (3.35 mg/ml)	-	Preservative-free eye drops/UD
FLUOROMETHOLONE/1	Flucon® (1 mg/ml)	-	Eye drops in vials/BAK
PREDNISOLONE/4	Solupred® (5 mg and 20 mg)	-	PO
	Cortancyl® (1 mg, 5 mg and 20 mg)	-	
METHYLPREDNISOLONE/5	Solumedrol® (500 mg or 1 g)	-	IV
TRIAMCINOLONE/5	Kenacort® (40 mg/1 ml and 80 mg/2 ml)	-	Localised injections
	Cidermex® (0.1%)	Neomycin	Ointment/Vaseline-Paraffin
BETAMETHASONE/24	Celestene® (4 mg/1 ml and 5.70 mg/ml)	-	Localised injections - PO - IV
DEXAMETHASONE/25	Chibrocadron® (5 mg/5 ml)	Neomycin	Eye drops in vials/BAK
	Dexafree® (1 mg/ml)	-	Eye drops in UD/Preservative free
	Frakidex® (0.1%)	Framycetin	Eye drops in vials/BAK Ointment/Vaseline-Paraffin
	Maxidex® (0.1%)	-	Eye drops in vials/BAK
	Maxidrol® (0.1%)	Polymixin B Neomycin	Eye drops in vials/BAK Ointment/Vaseline-Lanolin
	Ozurdex® (700 µg)	-	Vitreous injectable implant/ Coglycolic polylactic acid
	Sterdex® (0.267 mg/single dose)	Oxytetracycline	Ointment/Titanium Dioxin
	Tobradex® (0.1%)	Tobramycin	Eye drops in vials/BAK

Classification of steroids used in ophthalmology[5].

BAK: benzalkonium

However, beyond their anti-inflammatory potency, the clinical anti-inflammatory activity of corticosteroids depends on many parameters[4]:

- corneal penetration capacity, which is greater with acetate than with phosphate groups,
- concentration,
- duration of action,
- and installation frequency, although above a certain frequency, has an observed threshold effect.

Therefore, **anti-inflammatory activity is not automatically correlated with corticosteroid potency:**

- Experimental studies have shown that 0.1% fluorometholone has a potent anti-inflammatory effect, equivalent to 1% prednisolone (not available in France), in the cornea[6].
- A randomised study showed that hydrocortisone ophthalmic ointment (not available in France) was significantly more effective on inflammatory signs and symptoms at concentrations of 2.5% and 1% than at concentrations of 0.5%[7].

3 | SIDE EFFECTS OF OPHTHALMIC CORTICOSTEROIDS

SIDE EFFECTS OF TOPICAL CORTICOSTEROIDS[8]

- Reduced resistance to viral, mycotic and bacterial infections;
- Herpes viral reactivation;
- Posterior subcapsular cataract;
- Ocular hypertonia;
- Delayed wound healing;
- Ulceration (corneal, scleral);
- Hypersensitivity (local, systemic).

3.1 | CORTICOSTEROID-INDUCED OCULAR HYPERTONIA

The precise mechanism of corticosteroid-induced intraocular pressure (IOP) increase has not been clarified, but the fact that cortisone induces profound changes to the trabecular architecture is well known, resulting in decreased aqueous humour outflow[9] due to increased resistance to trabecular aqueous humour outflow in the corneoscleral and cribriform trabeculae. Corticosteroid-induced ocular hypertonia can occur at any age, including in children[10].

The population can be divided into 2 categories:

- A minority of “corticosteroid respondents” in whom moderate to severe hypertonia occurs.
- “Non-respondents” who do not show a hypertonic response to steroids. After 4 to 6 weeks of daily corticosteroid therapy in the general population, 4 to 6% of patients are “high respondents” with a pressure increase to more than 15 mmHg.

Approximately one-third are “moderate respondents” with pressure increases at between 6 and 15 mmHg and two-thirds have no IOP increase or an increase of less than 6 mmHg and are considered as “non-respondents”[11].

Several risk factors have been identified[12] :

- Primary open-angle glaucoma

  Approximately 30% of patients at risk for glaucoma and 90% of patients with documented glaucoma are likely to develop elevated IOP on corticosteroid therapy, including first-degree relatives of patients with glaucoma.

  Conversely, glaucoma-free subjects with a high-pressure response to corticosteroid therapy appear to have an increased risk of developing subsequent spontaneous glaucoma.

	STRONG HYPERTONIA	INTERMEDIATE HYPERTONIA	NO HYPERTONIA
GENERAL POPULATION	5%	35%	60%
PRIMARY OPEN-ANGLE GLAUCOMA	90%	10%	0%
PRIMARY OPEN ANGLE GLAUCOMA FAMILY	30%	50%	20%
DESCENDANTS OF THOSE PRIMARY OPEN-ANGLE GLAUCOMA	25%	70%	5%

Incidence and intensity of corticosteroid-induced ocular hypertonia[12]

- High myopia, transfixing keratoplasty, refractive surgery, LASIK, Descemet Stripping Automated Endothelial Keratoplasty (DSAEK)

In these situations, the corticosteroid-induced increase in IOP is masked by a thin central cornea, changes in ocular rigidity, corneal oedema and fluid accumulation under the LASIK flap.

- Children under 10 years of age and the elderly

Children have a particularly high risk of cortisone-induced glaucoma: about one-fifth of children treated with local corticosteroids develop glaucoma, often with an earlier onset and faster progression than in adults, with more significant glaucomatous changes[13].

- Diabetes mellitus or connective tissue disease, particularly rheumatoid arthritis[12]
- Pigment dispersion syndrome or post-traumatic angle recession[12]
- Endogenous hypercorticism[12]

The route of administration of corticosteroids influences the risk of ocular hypertonia: systemic treatments have a lower risk than topical treatments. Peri-ocular injections are the most dangerous route due to their prolonged duration of action[11].

Dexamethasone 0.5% (not available in France) administered topically 3 times a day for 4 weeks causes an increase in IOP in normal subjects, from 6 to 10 mmHg in 30% of cases (intermediate respondents) and more than 15 mmHg in 5% of cases (high respondents). An increase of at least 6 mmHg occurs in 95% of glaucoma patients[9]. In patients with intravitreal implants, dexamethasone causes an IOP increase of more than 10 mmHg in 12 to 15% of patients[12].

The intravitreal injection of triamcinolone is accompanied by an IOP increase of several millimetres of mercury in 50% of patients. It increases in 22% to 60% of patients if the pre-treatment IOP is less than or more than 15 mmHg[12]. It is important to note that a pressure increase in response to peri-ocular corticosteroid injections does not correlate with the increase or lack of increase observed with a previous topical treatment.

The IOP increase is also directly proportional to the anti-inflammatory potency and corticosteroid concentration and is based on intraocular penetration[12]. Thus, prednisolone (not available in France), betamethasone and dexamethasone, which are potent corticosteroids, are more likely to induce hypertonia than lower potency compounds[11].

Ocular hypertonia usually occurs within the first few weeks of treatment with more potent corticosteroids and after a few months with less active compounds. However, it can sometimes occur in the early hours or after several years of chronic treatment[12].

Discontinuing corticosteroid therapy, which should be done as soon as an increased IOP is observed, usually allows for the IOP to normalise within 1 to 4 weeks. In rare cases, the IOP remains elevated despite the discontinuation of corticosteroids and an anti-glaucoma treatment may be necessary[12]. It would appear that the corticosteroid therapy treatment duration influences the reversibility of ocular hypertonia[12]. If corticosteroid therapy must be continued, it is prudent to consider a less hypertonic compound, to recommend non-steroidal anti-inflammatory agents or to combine immunosuppressants in order to reduce the administered corticosteroid load[9].

3.2 | CORTISONE-INDUCED CATARACTS

Corticosteroid-induced cataracts have 3 characteristics: they are only associated with steroids with a glucocorticosteroid activity; they involve the aberrant migration of lens epithelial cells; they are located centrally in the central posterior subcapsular region,[14] and also bilaterally, although they are commonly asymmetric[15].

Although the mechanisms of cortisone-induced cataract induction remain unknown, it is assumed that a key role is played by glucocorticosteroid receptor activation leading to changes in the transcription of specific genes. Glucocorticosteroid receptor activation is associated with many proliferation, suppression of differentiation cells, with a reduced sensitivity to apoptosis, with alterations in trans-membrane exchange and with an increase in oxygen reactive species.

The glucocorticosteroid receptor may also have indirect effects, and could thus affect the lens indirectly through other cells in the ocular compartment or even in a more distant location. Finally, the assumption that glucocorticosteroids bind to lens proteins, therefore producing steroid-protein adducts, cannot be ruled out[14].

Cortisone-induced cataracts occur after the prolonged administration of corticosteroids. Their occurrence depend mainly on the cumulative dose as well as on the route of administration, the dose, the treatment duration, the extent of ocular inflammation and the patient's age[4]. The risk of developing a cortisone-induced cataract also depends on the intraocular penetration of the corticosteroid. However, even compounds with low intraocular penetration can cause iatrogenic cataracts after several months of administration[11].

There are no preventive measures against cortisone-induced cataracts, and they do not regress when treatment is discontinued[15].

3.3 | RISK OF INFECTION

Corticosteroids cause a decrease in immune defences, especially against infectious agents, and promote bacterial, viral and fungal infections. **They are contraindicated in cases of active herpetic epithelial damage, mycosis and all forms of bacterial infections not controlled by anti-infection agents[8].**

The administration of corticosteroids in active herpetic ocular infections can worsen the prognosis and even lead to corneal perforation. The possibility of reactivating a latent herpes infection via systemic corticosteroid therapy has been demonstrated in experiments on animals[10].

The virus' replication cycle resumes and may trigger herpetic keratitis. In some cases, viral replication is massive, as in geographic epithelial forms or necrotic stromal forms, whereas it is more limited in simple dendrites or non-necrotic stromal forms[16].

Bacterial keratitis is promoted by any form of immunosuppression, including prolonged treatment with topical corticosteroids. Topical corticosteroid therapy may be associated with an increased incidence of Pseudomonas corneal ulcers, active *Chlamydia trachomatis* infections and fungal keratitis. A risk of Candida endophthalmitis has been reported with systemic corticosteroid therapy[17].

Keratomycosis is promoted by local or systemic immunosuppression. Local corticosteroids are recognised to have a very negative effect on its progress[18]. One case of purulent corneal melting secondary to a poly-resistant Fusarium oxysporum infection was described, the only risk factor being 7 days of local corticosteroid therapy[19].

However, the anti-inflammatory effect of corticosteroid therapy may be useful in some infections when combined with anti-infection agents, in which case the corticosteroid is given after sufficient time has elapsed to demonstrate the efficacy of the anti-infection treatment (see next chapter, "Which corticosteroids should be used for which situation?")

3.4 | DELAYED WOUND HEALING

Experimental studies on animals performed in the 1980s revealed abnormalities in corneal healing under the effect of corticosteroids: healing delay proportional to the administered dose[20], reduced healing resistance and collagen formation[21].

Various experimental studies have subsequently reported conflicting results in this area, showing either an increase or decrease in healing resistance or a lack of corticosteroid effect in either direction[22]. More recently, a new experimental study reported that dexamethasone improved the resistance of a corneal healing after 7 days compared to untreated corneal incisions, but after 21 days, the corneas treated with corticosteroid or NSAIDs were significantly more fragile than untreated incised corneas. The early effect is believed to be related to corticosteroids' reduction of stromal inflammation and the release of proteolytic enzymes promoting re-epithelialisation, and the late effect is believed to be due to the inhibition of fibroblast and collagenase activation[22].

Corticosteroids modify the expression of many genes in the corneal epithelium and experimentally cause delayed healing through the inhibition of cell migration. However, this delay does not appear to be unambiguously deleterious, as it is accompanied by improved tight junction integrity and thus the ability of the epithelium to act as a barrier[23].

3.5 | PERFORATION

Thinning of the cornea and sclera may increase the risk of corneal melting and subsequent perforation when using local corticosteroids[24]. Such an effect has already been described, particularly in cases of infectious keratitis[8, 16, 19], corneal burns[8] or systemic autoimmune disease (rheumatoid arthritis, lupus, Sjögren's syndrome, etc.)[25].

However, as topical corticosteroids make up part of the treatment for some of these conditions, their use must be cautious and respect the limits defined by clinical studies (see the chapter below: "Which corticosteroids should be used for which situation?").

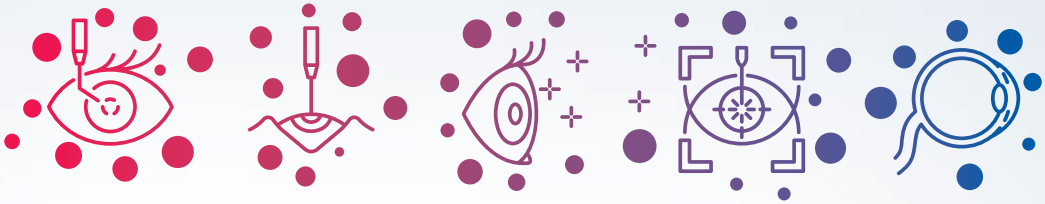
3.6 | SYSTEMIC SIDE EFFECTS

The topical or intravitreal delivery of corticosteroids (injections, implants) usually does not result in a significant systemic effect due to minimal plasma uptake. However, there is a risk in very young children: in a retrospective series on 26 children under 2 years of age receiving topical corticosteroid eye drops after congenital cataract surgery, corticotropic insufficiency was observed in two-thirds of the patients with 2 cases of clinically evident Cushing's syndrome[26]. A case of Cushing's syndrome was described in a 9-year-old child after 6 months of treatment with corticosteroid eye drops[27].

Peri-ocular injections, on the other hand, are accompanied by the rapid and almost complete passage of the injected corticosteroid into the plasma, the hyperglycaemic effects were comparable to those of an intravenous bolus. The risk of acute side effects after a peri-ocular injection is theoretically comparable to that of an intravenous bolus given the identical plasma concentrations and the observed hyperglycemic effects. Therefore, we must apply the same care when identifying risk areas and during monitoring: patients with heart disease or with a high cardiovascular risk, diabetics, immunocompromised patients, patients with a history of an allergic reaction to corticosteroids[28]. The main potential acute systemic effects of corticosteroids are: fluid retention, hypertension, heart failure, hypokalemia, dyslipidemia, infections, arousal, insomnia[4]...

PART II:

WHICH CORTICOSTEROIDS SHOULD BE USED FOR WHICH SITUATION?



1 | OCULAR SURFACE DISORDERS

KEY POINTS ON THE PROPER USE OF CORTICOSTEROIDS[8]

- The type and location of the inflammation determines the appropriate route of administration.
- The anti-inflammatory potency of the corticosteroid must be adapted to the condition being treated.
- The frequency of instillation should be reassessed frequently.
- The duration of corticosteroid treatment for mild ocular surface disease should not exceed 3 to 4 weeks.
- Corticosteroids should not be discontinued abruptly.
- Minimum effective doses should be used for the shortest possible length of time.
- Each patient should be treated according to the degree of inflammation.
- Follow-up should be carried out regularly and closely to assess the tolerability and efficacy of the treatment.
- Patient compliance should be regularly assessed.
- Systematic investigation of a medical history of ocular herpes is required.

PART II. WHICH CORTICOSTEROIDS SHOULD BE USED FOR WHICH SITUATION?

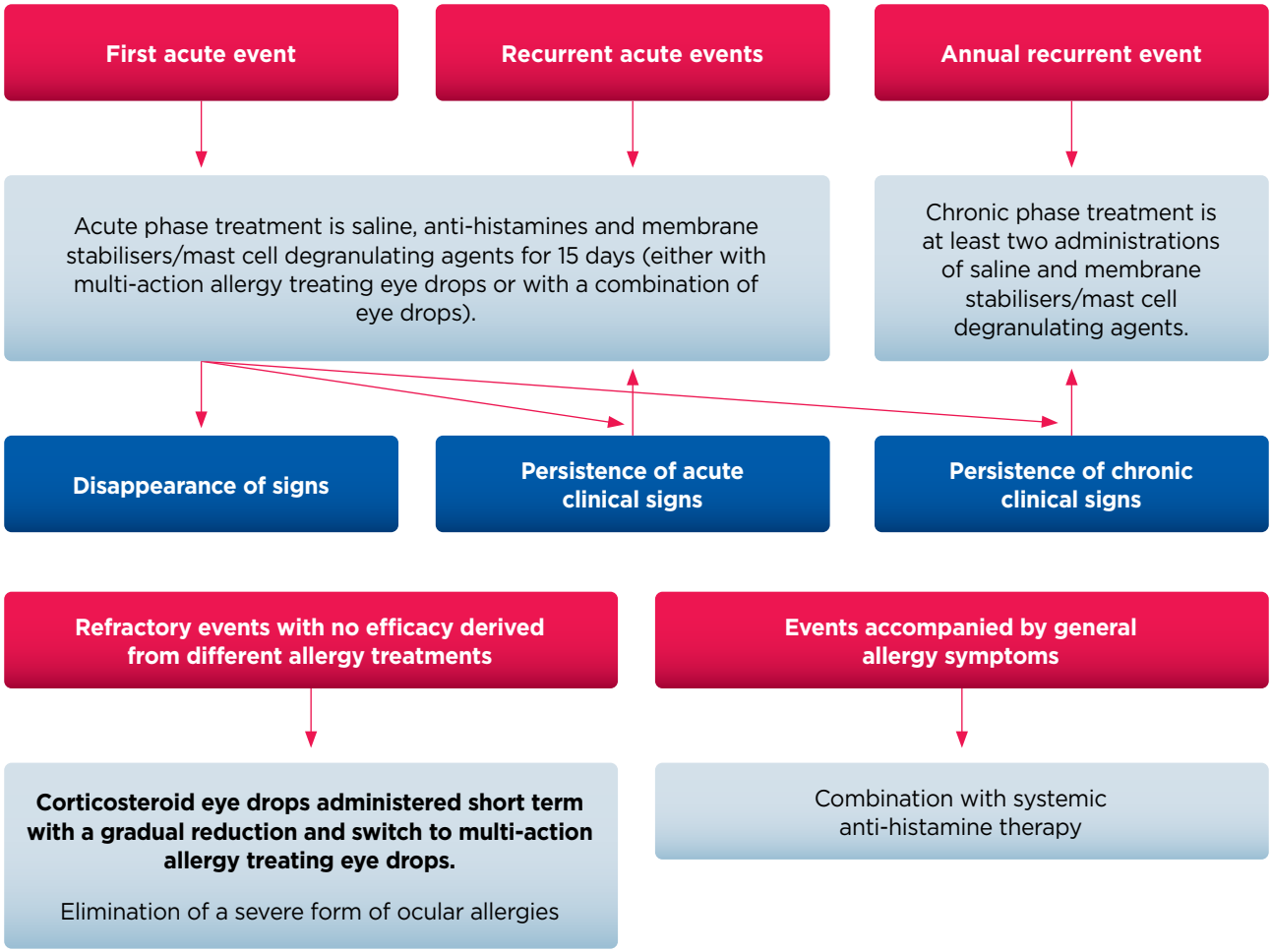
1.1 | ALLERGIC CONJUNCTIVITIS

Topical corticosteroids inhibit the production of various inflammatory mediators such as prostaglandins, which are released when the eye reacts to allergens[29]. At the cellular level, they increase the membrane density of beta-adrenergic receptors, which reduces mast cell degranulation, reduces chemokine production and thus the migration of eosinophil and lymphocyte inflammation cells. They have no effect in the acute phase (they do not prevent histamine release), but they essentially have an effect in the late phase by reducing leukocyte tissue infiltration[30].

The basis of treatment remains avoiding the allergen in the first place. If this is not possible, preservative-free eyewash solutions should be initiated. After this, using a topical and systemic anti-histamine 1 (anti-H1) (in the event of nasal manifestations) will calm the pruritus and the rashes.

Corticosteroid instillation may be used in year-round and seasonal allergies that become more severe. Their only benefit is that they more rapidly decrease chemosis. They should be used as short-term curative treatments. In this context, hydrocortisone 0.1% (dosage not available in France) has shown its efficacy in rapidly reducing the signs and symptoms from allergies[31,32].

The use of topical corticosteroids to treat allergic conjunctivitis is only recommended for severe forms of allergic conjunctivitis that do not respond to standard treatment and only for over the short term.



Therapeutic strategy for the treatment of acute, year-round and seasonal allergic conjunctivitis[32]

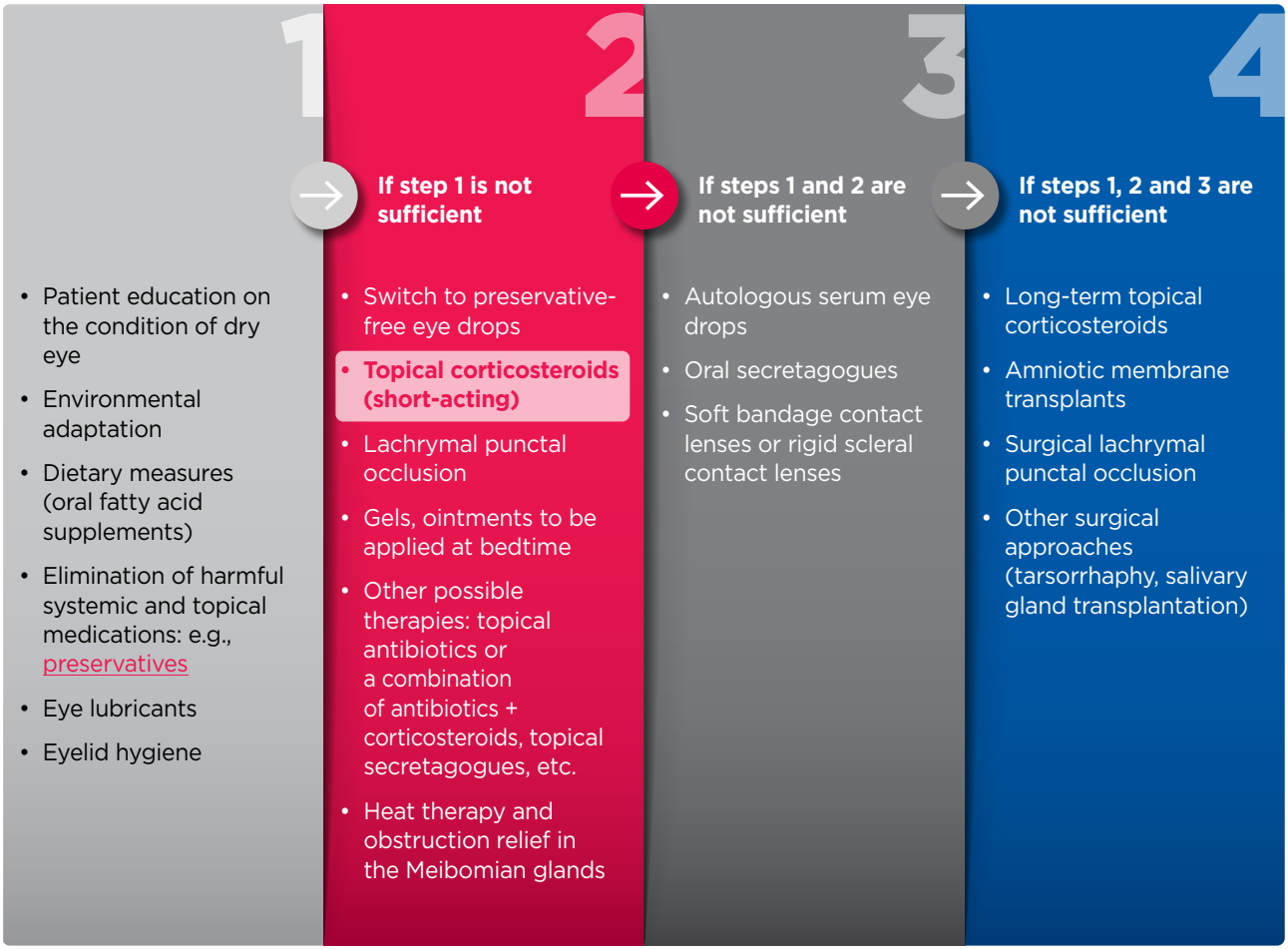
The treatment for vernal (VKC) and atopic (AKC) keratoconjunctivitis is much the same as the treatment for common allergic conjunctivitis, with the application of drug-free treatments being of paramount importance. In an emergency, the use of local corticosteroid therapy will compensate for any possible previous treatment insufficiency. Corticosteroid therapy is low potency over the short term, which is made necessary by a disability causing functional gene or dense keratitis[32].

1.2 | DRY EYES

Inflammation plays a very important role in the development and perpetuation of dry eye. Reducing it is therefore a real challenge and important in ending the disease's vicious cycle[33]. Therefore, any therapeutic solution that helps reduce inflammation in one or more components of the ocular surface should ultimately help improve the ocular surface's overall condition.

Thus the advantage of corticosteroids is their rapid anti-inflammatory effect, though they are not usually recommended for the treatment of the inflammatory component of dry eye. The recent use of hydrocortisone should allow this compound to be used as a short-term treatment during periods when the disease is resurging[34].

This is why the latest international consensus recommendations, the Tfos DEWS II, recommend the use of topical corticosteroids as short-term treatment as soon as initial management measures have failed[35].



Dry eye management according to the Tfos DEWS II[35]

Thus, preservative-free 0.335% hydrocortisone *(Softacort®, indicated for the treatment of moderate and non-infectious conjunctival pathologies with an allergic or inflammatory origin)* has been studied for short term treatments in recent randomised studies. Patients with chronic dry eye were treated with topical hydrocortisone for 2 weeks.

The various clinical signs were thus reduced. The patients' quality of life, as measured using the OSDI score, improved. Finally, during these studies, no increase in IOP was recorded[36, 37].

Finally, corticosteroids are particularly useful when initiating treatment with cyclosporine, the benefits of which often appear slowly and improve its tolerance[8, 33].

1.3 | BLEPHARITIS[38]

Topical corticosteroids are only indicated for acute immunologic inflammatory complications such as chalazion, corneal catarrhal infiltrates, or scleritis.

They should only be prescribed for a short period of time due to the risk of iatrogenic complications.

1.4 | ROSACEA[39]

The treatment of ocular rosacea is primarily based on palpebral hygiene: application of warm moist compresses; eyelid massage; artificial tears.

The drug treatments employed are cyclins per os for several months or macrolide per os, 3 days/week for 4 weeks, and a course of macrolide eye drops, 3 days/week for 4 weeks.

1.5 | HERPES INFECTIONS

Corticosteroids are contraindicated for epithelial damage, as they can worsen the clinical picture, for example; by transforming a single dendrite into geographic damage, and they should not be used in the event of necrotic damage as they may facilitate corneal melting[40].

However, corticosteroids may be useful in epithelial forms with stromal involvement, in non-necrotic stromal forms and in endothelial forms. The use of corticosteroids in herpes infections has been the subject of specific multi-centre studies, one of which is *the herpetic eye disease study* (HEDS). Visual acuity at 6 months was comparable with or without corticosteroids, but this study reported a much faster resolution and lower rate of persistence from herpetic stromal keratitis in patients treated with corticosteroids combined with antivirals compared to those treated with antivirals alone. Furthermore, whether corticosteroids are administered early or delayed by a few weeks has no influence on the disease progress[41].

It is common to start corticosteroids when an antiviral treatment has been clinically proven to be effective, partially improving symptoms or at least stopping the disease progress. The anti-viral treatment should be continued for at least the duration of the corticosteroid therapy.

Depending on the degree of urgency, they can be administered as an instillation (eye drops and ointment), as a subconjunctival injection (avoiding delayed forms) or even by intravenous infusion. Monitoring must be rigorous after treatment is initiated (verify that the disease is not becoming worse) and treatment withdrawal must be gradual to avoid a rebound effect[40].

1.6 | BACTERIAL KERATITIS

The use of corticosteroids for the treatment of infectious keratitis remains a controversial issue. Corticosteroids can limit tissue destruction and scarring caused by inflammation, but they can also delay healing and potentiate the infectious process[42].

A Cochrane review of 3 randomised trials as well as the large SCUT study concluded that the available evidence does not suggest a significant benefit of adjuvant corticosteroid therapy in the treatment of bacterial keratitis[43].

However, the subgroup analysis of the *Steroidal for Corneal Ulcers Trial* (SCUT) qualifies this result. The SCUT study is the largest randomised trial in this field, involving 500 patients with bacterial keratitis. Their results do not show a benefit over the entire study population at 3 months of corticosteroid therapy combined with appropriate antibiotic treatment, neither in terms of visual acuity, nor in terms of scar size, healing time or corneal perforation. However, a modest benefit was reported in a few of the study subgroups: in patients with very poor visual acuity at baseline or those with a central ulcer[44], and in patients who received early corticosteroid therapy, 2 to 3 days after the start of antibiotic therapy[45].

A mean improvement in visual acuity in one line was recorded at 12 months in patients who received a corticosteroid, with the exception of patients infected with Nocardia (atypical bacteria), who did not show any improvement. Scar size did not improve with corticosteroid therapy and it even increased in patients with the Nocardia infection[46]. In the subgroup of patients infected with *Pseudomonas aeruginosa*, there were no specific benefits or risks associated with the use of corticosteroids.

This study did not report any adverse outcomes related to the use of corticosteroids.

KEY POINTS FOR THE PROPER USE OF CORTICOSTEROIDS IN CORNEAL ABSCESSES[8]

- Contraindicated in cases of suspected fungal, mycobacterial, *Acanthamoeba* or herpetic viral infection.
- The culture is positive and the bacteria are identified.
- The bacterium is sensitive to prescribed antibiotics.
- The clinical picture has improved significantly since the use of antibiotics.

Topical corticosteroid therapy is initiated depending on the evolution and the causative germ:

- Gram+ bacteria identified: possible as of 24 to 48 hours of progress.
- Gram- bacteria: after 4 to 5 days depending on the size of the abscess, control of the infection and degree of associated inflammation.
- Amoebae: the use of corticosteroids is controversial, the minimum period before initiating corticosteroid therapy is 15 days.
- Fungi: any corticosteroid therapy is considered dangerous, especially in the acute phase of an infection[47].

1.7 | OTHER OCULAR SURFACE DISEASES

Epidemic viral keratoconjunctivitis

As topical corticosteroids prolong viral carriage, their use in viral keratoconjunctivitis is limited to severe early conjunctival complications, such as pseudomembranes, and later corneal complications associated with decreased visual acuity. In these cases, the therapeutic effect is the prevention of post-inflammatory fibrosis. Unfortunately, corticosteroid-dependence is most often the rule. Close monitoring is required to limit iatrogenic effects[8].

Thygeson's superficial punctate keratitis

Thygeson's superficial punctate keratitis is highly corticosteroid-sensitive but also constantly corticosteroid-dependent. This disease, which never leads to visual complications, except through corticosteroid-induced iatrogeny, **should not be treated with corticosteroids, save in extremely limited cases[8].**

Chemical burns

Corticosteroids should be used in the early stages of chemical burns caused by bases as they improve disease prognosis by decreasing the infiltration of inflammatory cells and secondary corneal damage (neovessels, fibrosis). Topical corticosteroids are associated with an increased risk of corneal and scleral melting due to a decrease in cellular anabolism in in favour of catabolism. These effects are partly counteracted by the combined use of ascorbic acid and doxycycline[8].

Corticosteroids have a beneficial anti-inflammatory effect in the treatment of corneal burns, but they also slow down epithelial and stromal repair. As the stromal repair phase is only activated after the 10th day, topical corticosteroids can be used under supervision during the first week.

They should be discontinued after the first week. They may be reintroduced after the 6th week if the inflammatory reaction persists, but their prolonged and continuous use is not recommended[48].

2 | NON-INFECTIOUS UVEITIS[49]

Topical corticosteroids with a strong anti-inflammatory action are the standard of care for anterior segment inflammation. In the event of severe and/or persistent inflammation, corticosteroids can be administered as a subconjunctival injection.

In the event of posterior uveitis or severe panuveitis, systemic corticosteroid therapy is required, by intravenous bolus that is then switched to oral administration, after ruling out any infectious pathology. Local corticosteroids are therefore adjuvant treatments administered by subconjunctival, posterior subtenonal or peribulbar injections delivering high intraocular concentrations. A subconjunctival injection of 2.5 mg of dexamethasone results in an intravitreal concentration of corticosteroids three times higher than that obtained after the peribulbar administration of 5 mg of dexamethasone and 12 times higher than the oral administration of 7.5 mg of dexamethasone.

Intravitreal corticosteroid injections or an intravitreal implant may be used for cystoid macular oedema that is resistant to systemic corticosteroid therapy and periocular injections.

Intra- or peri-ocular corticosteroid injections should be avoided, if possible, in children and non-presbyopic adults, particularly with repeated injections.

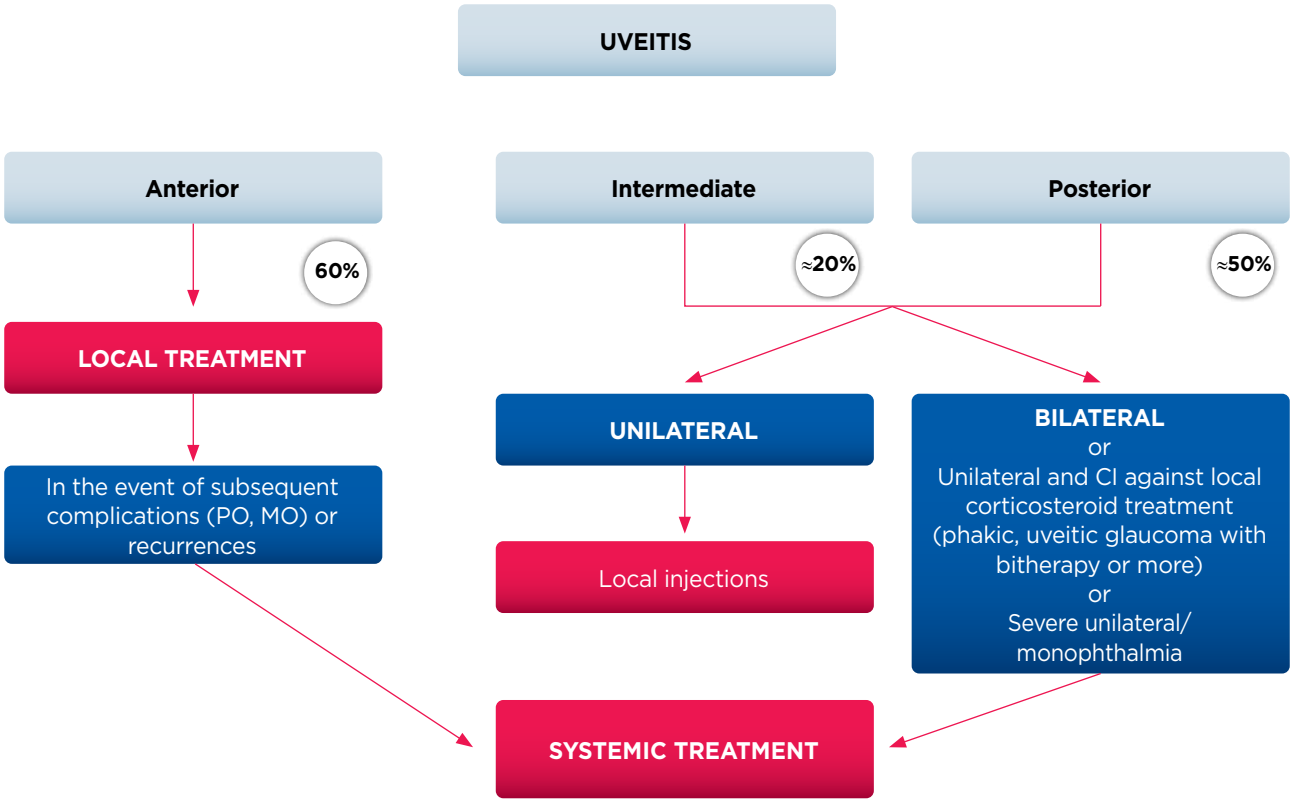
PART II. WHICH CORTICOSTEROIDS SHOULD BE USED FOR WHICH SITUATION?

The longer the systemic corticosteroid therapy is tapered and the more the uveitis is severe, the slower the therapeutic response and/or the more frequent the inflammatory rebound.

If the uveitis does not resolve with high doses of corticosteroids (1 mg/kg/day), an infectious cause or pseudo uveitis, such as vitreoretinal lymphoma, should be systematically investigated again.

In the event that the recurrence increases (corticosteroid dependence), the use of cortisone-sparing treatments should be discussed in adults and are essential in children.

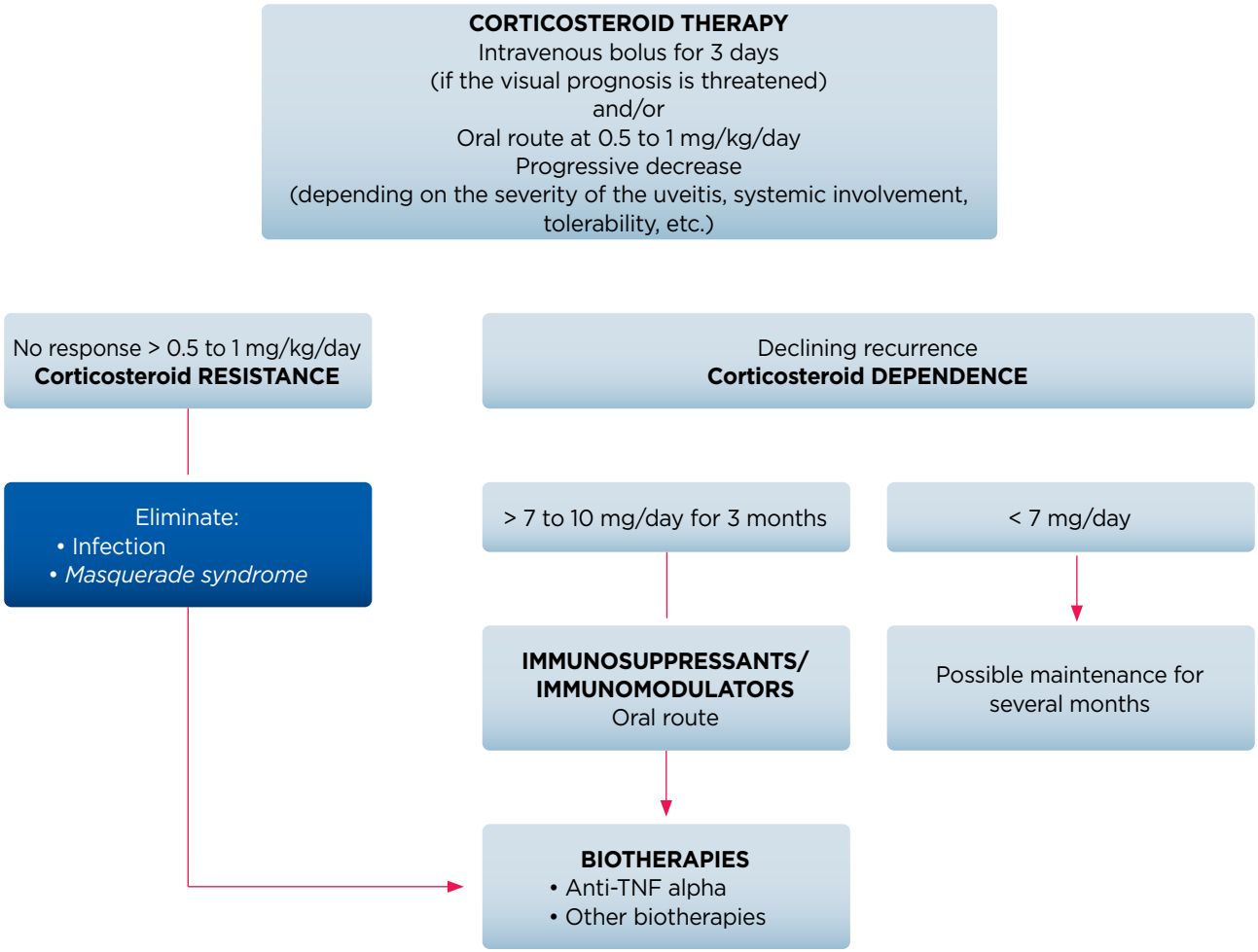
A list of autoimmune or auto-inflammatory disease and rare disease reference centres in ophthalmology is indicated in the 2020 National Care Protocol.



CI: contraindications - MO: macular oedema - PO: papilloedema

Simplified treatment algorithm for non-infectious uveitis[50]

PART II. WHICH CORTICOSTEROIDS SHOULD BE USED FOR WHICH SITUATION?



Therapeutic principles of corticosteroid therapy in non-infectious uveitis[50]

GUIDELINES FOR MONITORING PATIENTS WITH UVEITIS DURING THE COVID-19 PANDEMIC

The SFO developed specific recommendations on this topic in March 2020[51]. In summary:

- Anti-infective, corticosteroid and/or immunosuppressant and/or biotherapeutic treatments should not be discontinued in patients with a suspected Covid-19 infection as severe inflammatory rebound may occur, requiring even higher doses of steroids.
- The initiation of local corticosteroid therapy is not contraindicated in the context of the pandemic, though a very slow decrease is preferred in order to avoid inflammatory rebound.
- In the event of fever, cough or respiratory signs in a patient taking systemic corticosteroids or immunosuppressants or biological agents: consultation, SARS-CoV-2 sampling and transient cessation of immunosuppressant and/or biological treatments with the maintenance of light corticosteroid therapy to be discussed on a case-by-case basis.
- In the event of uveitis requiring corticosteroids and/or immunosuppressants and/or biological agents, it is preferable to delay the initiation of systemic therapy in at risk or COVID+ patients. In the event of a direct threat to the subject's vision, local administration should be favoured.

3 | POST-SURGERY

3.1 | ENDOCULAR SURGERY: CATARACTS, RETINA, GLAUCOMA

All types of surgery cause inflammatory responses. In the case of endocular surgery, uncontrolled inflammation can lead to complications such as posterior synechiae, uveitis, secondary glaucoma or cystoid macular oedema (CMO)[52].

Postoperative macular oedema can occur after cataract surgery, (Irvine-Gass syndrome) or after any other endocular surgery[53]. It is the most common cause of visual impairment after cataract surgery, and its incidence seems to correlate with the magnitude of postoperative inflammation[52].

Cataract surgery

The evolution of surgical techniques over the last few decades has made it possible to reduce the extent of surgical trauma and thus limit postoperative inflammation, as well as reducing the incidence of CMOs, which is currently 1 to 2% after uncomplicated age-related cataract surgery[53]. However, the risk of CMO remains significantly higher, at around 10%, after cataract surgery in diabetic patients or after surgery for retinal detachment.

Thus, the use of local anti-inflammatory agents in the perioperative period remains relevant. Such an attitude, validated for the prevention of MO in diabetics after cataract surgery, should probably be applied to vitreoretinal surgery, even if it has not yet been validated by the literature[53].

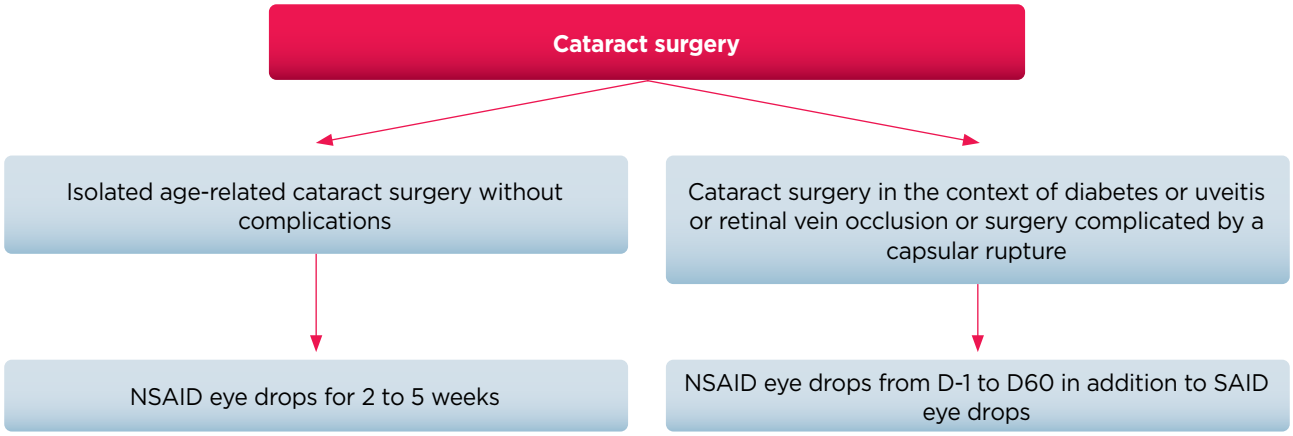
The anti-inflammatory efficacy of NSAIDs alone in cataract surgery is superior to that of corticosteroids alone,[52, 54, 55, 56] a combination of NSAIDs + corticosteroids is more effective than corticosteroids alone,[57, 58] and there is likely to be synergy between NSAIDs and corticosteroids[59, 60, 61].

Preventive treatment depends on the surgery and, especially, the terrain:

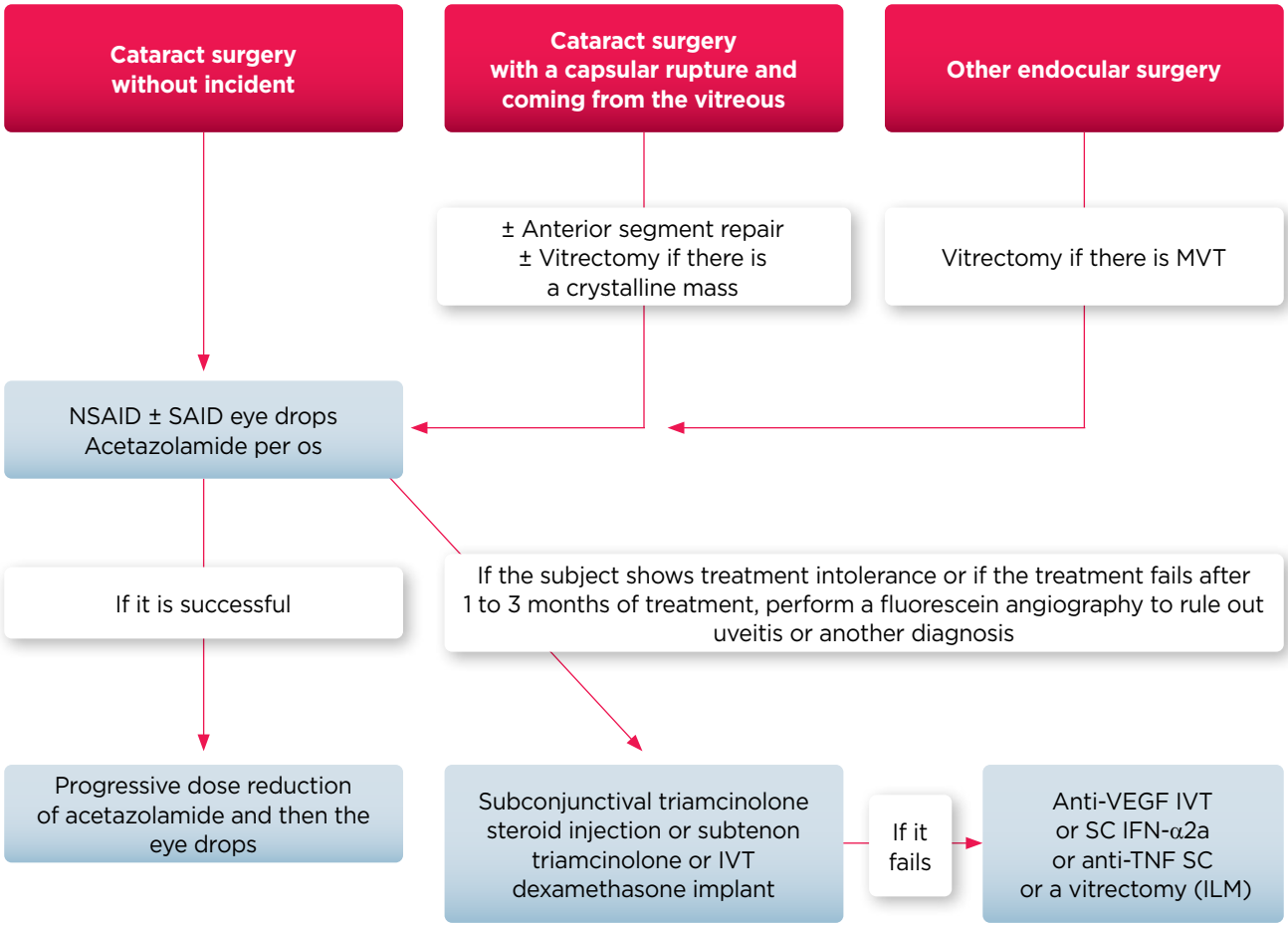
- In the case of isolated age-related cataract surgery with no ocular or systemic disease having ocular repercussions: NSAID eye drops are the standard of care, initiated, if possible, 48 hours before the surgery and continued for 15 days to 4 weeks[53]. Corticosteroids are not superior to NSAIDs in reducing postoperative inflammation and are significantly inferior to NSAIDs in preventing Irvine-Gass syndrome[52].

- In the case of cataract surgery in a young patient, a diabetic patient or on an eye with (or with a history of) uveitis, scleritis or venous occlusion, treatment is still based on a combination of corticosteroid eye drops and NSAIDs, sometimes combined with the resumption or reinforcement of systemic steroid treatment, particularly in patients with active or former uveitis or scleritis. Due to a high risk of Irvine-Gass syndrome in diabetic patients, it is recommended that the administration of NSAIDs be continued for 2 to 3 months[53].

PART II. WHICH CORTICOSTEROIDS SHOULD BE USED FOR WHICH SITUATION?



Preventive treatment of postoperative macular oedema[53]



Curative treatment of postoperative macular oedema[53]

PART II. WHICH CORTICOSTEROIDS SHOULD BE USED FOR WHICH SITUATION?

Glaucoma surgery

During the perioperative period of filtration surgery, inflammation causes an excessive scarring response, characterised by inflammation, fibroblast proliferation and extra-cellular matrix production at the cellular level[62]. The formation of conjunctival fibrosis circumscribing the filtration bulla is the main cause of trabeculectomy failure[63].

Thus, controlling inflammation is crucial in the perioperative period.

There is frequently sub-clinical preoperative conjunctival inflammation, connected with preservatives used in multiple types of anti-glaucoma eye drops that are usually administered at this stage of glaucoma. This inflammation represents a poor prognostic factor regarding the effectiveness of filtration surgery.

Reducing exposure to preservatives[64] and administering a steroidal or non-steroidal anti-inflammatory eye drop for 1 month can reduce preoperative inflammation[65].

Post-operatively, the fight against excessive fibrotic scarring calls for anti-inflammatory treatment, as well as anti-metabolic treatment, which must be continued in a significant and adapted manner[63]. A recent experimental study reported that the combination of corticosteroids and mitomycin A had a synergistic effect, with a larger filter bubble, and a reduction in inflammatory infiltrates and neovascularisation, compared to each individual compound used as a monotherapy[66].

The use of steroidal anti-inflammatory agents is indicated to limit the inflammatory reaction of the conjunctiva tenon tissue. This inflammation lasts from several weeks to several months, and corticosteroid therapy should be continued for 6 to 12 weeks at progressively decreasing doses when there is no corticosteroid-induced hypertonia[63].

3.2 | CORNEAL SURGERY

Refractive surgery

An inflammatory reaction occurs early, within 48 to 72 hours after photorefractive keratoplasty, and, in some patients, may result in an abnormal healing response, particularly in highly myopic patients. **Thus, the modulation of inflammation during the first 3 days post-surgery could prevent the complications from developing, and it is common to prescribe corticosteroids during this short period[67].**

As early as 1992, in a randomised, double-blind, placebo-controlled study of 113 refractive surgery patients, Gartry et al. reported a better refractive outcome at 6 weeks in patients receiving corticosteroid eye drops (-3.00 vs. -6.00 D respectively). However, this benefit was no longer significant after the corticosteroid therapy was discontinued at 3 months. There was no significant effect observed on corneal haze or the visual parameters[68].
However, experiments on animals have shown a transient reduction in haze under the effects of corticosteroid therapy, which disappears when the treatment is discontinued[69].

Other clinical studies have also shown either a beneficial effect on the refraction of corticosteroids used over several months, disappearing when the treatment is discontinued[70].

Another double-blind randomised study in 2001 compared corticosteroids and an NSAIDs, administered for 3 days immediately after 80 photorefractive keratoplasties. There was no delayed healing observed and the re-epithelialisation time was 3 days for the majority of patients, which was similar for the two products. In the corticosteroid group, more patients had transient secondary hyperopia and, in the NSAID group, more patients had myopic regression at 3 and 12 months after surgery.

But overall, 90% of patients achieved the targeted correction of ±1D in the corticosteroid group, compared to 70% in the NSAID group, which is a statistically significant difference. At 1, 6 and 12 months, corneal haze was significantly diminished in the corticosteroid group, particularly in patients with high myopia[67].

Thus, short-term corticosteroid therapy appears to be of benefit immediately after refractive surgery.

In addition, diffuse lamellar keratitis (KLD) is a complication of LASIK, involving non-specific inflammation of the interface. Mild KLD is usually highly corticosteroid-sensitive and responds well to aggressive, hourly topical corticosteroid therapy. More severe cases require the use of oral corticosteroids with or without a local corticosteroid or interface irrigation[71]. A retrospective study showed that the treatment, or prevention in at-risk patients, of severe diffuse lamellar keratitis with oral and local corticosteroids resulted in a good visual outcome, with a deviation from the desired correction of 0.14 dioptres +/- 0.53, without corneal scarring or permanent loss of visual acuity. The average treatment duration was 18 days (adjusted for the KLD progression, 7 to 28 days for local treatment and 4 to 45 days for systemic treatment with rapid dose reduction). None of the 22 treated eyes required a flap lift or interface irrigation[72].

Corneal transplant[8, 73]

Slowly tapering topical corticosteroid therapy over a period of 1 to 2 years is the gold standard for the prevention of corneal graft rejection.

The Collaborative Corneal Transplant Study (CCTS) has shown that intensive topical corticosteroid therapy combined with regular monitoring reduces the rate of rejection, including in high-risk transplants[8].

If there is a high risk of rejection, local corticosteroids should be started the day before the transplant and continued every hour in the immediate postoperative period, with a very gradual dose decrease. Maintaining local corticosteroid therapy for several years may be considered.

Systemic corticosteroid therapy using an IV bolus with rapid dose reduction is only indicated in the treatment of acute rejection. Oral corticosteroid therapy has not been shown to be of value in preventing or treating rejection.

Corticosteroid-induced glaucoma is harmful to the optic nerve as well as to the survival of the graft, and the difficulty in treating glaucoma with keratoplasty sometimes requires substitution with a less hypertonic, but often less effective, corticosteroid.
By decreasing epithelial healing, corticosteroids may promote persistent epithelial defects.
Corticosteroids and ocular surface disorders increase the risk of infection. Microcrystalline keratopathy, specific to corneal transplants, is a transplant infection without inflammation.

Immunotherapy can be combined with local steroids if there is a high risk of rejection or substituted for corticosteroids if the latter cannot be continued due to side effects.

PART III:

AT-RISK POPULATIONS

1 | MANAGEMENT IN CHILDREN

In children, long-term continuous treatment with corticosteroids can cause adrenal insufficiency[24].

Furthermore, ocular hypertension associated with the use of topical corticosteroids is more frequent, more severe and more rapid in children than that reported in adults[12, 24].

A recent study reported that out of 1,423 young patients with VKC, 240 of which used topical corticosteroids chronically. Children with VKC are particularly at risk for corticosteroid dependence due to the achievement of rapid symptom relief with this therapeutic group. Out of 240 patients, 47 (92 eyes) had corticosteroid-induced ocular hypertonia, an average of 38 ± 12 mmHg. At least 1/3 of these patients had an impaired cup-to-disc ratio and/or visual field. The IOP could be normalised just by discontinuing corticosteroid therapy in only 9 eyes, and with drug treatments in 27 eyes. A trabeculectomy was necessary in 2/3 of the eyes[74].

Therefore, long-term continuous treatment with corticosteroids should be avoided in children.

2 | MANAGEMENT OF PREGNANT WOMEN

There is little or no data on the use of topical ophthalmic corticosteroids in pregnant women. Corticosteroids cross the placenta.

Animal studies have shown reproductive toxicity with the formation of cleft palates. The clinical relevance of these observations is unknown. Effects on the foetus/newborn have been reported (intrauterine growth retardation, inhibition of adrenal cortical function) after the systemic administration of corticosteroids at higher doses. However, these effects have not been reported in ophthalmic use[24].

The available data on topical corticosteroids are related to percutaneous administration. Studies in this area do not show a teratogenic effect or an increased risk of foetal death or prematurity, but intrauterine growth retardation is possible with the most potent corticosteroids[75]. Therefore, compounds with low or moderate activity would be preferable[76].

However, the use of topical corticosteroids is not recommended during pregnancy unless absolutely necessary[24].

3 | MANAGEMENT IN THE ELDERLY

Caution should be exercised in elderly patients who often carry several risk factors for corticosteroid therapy complications: cardiovascular history, diabetes, immunodepression[28]... and especially glaucoma.

4 | MANAGEMENT IN PATIENTS WHO WEAR CONTACT LENSES

Contact lenses, especially soft lenses, are the number one risk factor for infectious keratitis in the developed world, particularly the *Pseudomonas infection*[77]. Fungal keratitis is rare but serious and is promoted by corticosteroids[18].

Contact lenses should not be worn during treatment with eye drops that contain corticosteroids[24].

CONCLUSION

We currently have therapeutic solutions available to combat inflammation on the ocular surface. Inflammation is omnipresent in many pathologies: from allergies to uveitis without forgetting dry eye, which has recently been recognised as an inflammatory disease. The therapeutic arsenal we have at our disposal allows for a real increase in the range as the severity of the inflammation increases, with the ultimate goal of restoring the ocular surface's homoeostasis. This review shows the role of corticosteroids in these surface inflammatory diseases as well as in ocular surgery, where the management of inflammation remains a challenge. The recent arrival of new compounds will make it possible to circumscribe and limit the side effects from anti-inflammatory drugs, the use of which is a major asset to ophthalmologists.

DEXAFREE® SAFETY DATA

Dexamethasone 1 mg/ml eye drops in single-dose containers:
Treatment of non-infectious inflammatory conditions in the anterior segment of the eye. Topical corticosteroids should never be prescribed for undiagnosed eye redness. DEXAFREE® should not be used in patients with infectious diseases or only after the infection has been controlled by effective therapy against infection.

CONTRAINDICATIONS

- Ocular infections not controlled by treatments against infection, such as:
  - acute purulent bacterial infections, including Pseudomonas and mycobacterial infections,
  - fungal infections,
  - amoebic keratitis,
  - epithelial keratitis due to herpes simplex virus (dendritic keratitis), a vaccine virus, the varicella-zoster virus and most other viral infections of the cornea and conjunctiva.
- Corneal perforation, ulceration and injury associated with incomplete re-epithelialisation.
- Known glucocorticoid-induced ocular hypertension.
- Hypersensitivity to the active ingredient or to any of the excipients.

WARNINGS AND PRECAUTIONS FOR USE

Patients should be monitored at frequent intervals for the entire treatment duration. The use of corticosteroids can lead to:

- Ocular hypertension/glaucoma (especially in patients with a previous intraocular pressure increase due to corticosteroids, pre-existing elevated intraocular pressure or glaucoma) as well as cataract formation with prolonged use, especially in children and the elderly.
- Opportunistic ocular infections whose signs and symptoms may be enhanced, aggravated or masked by topical ocular corticosteroids.

Dexamethasone should only be used if NSAIDs are contraindicated. For patients with:

- Corneal ulcerations: no topical dexamethasone, except when inflammation is the main cause of delayed healing and when an appropriate aetiological treatment has already been prescribed. Close and regular monitoring by an ophthalmologist is necessary.
- Thinning of the cornea and sclera: increased risk of perforation is possible with local corticosteroids.
- Corneal calcifications: at the first sign, the eye drops should be discontinued and replaced with a phosphate-free eye drop. Indeed, corneal calcifications requiring transplantation have been reported in patients treated with phosphate-containing ophthalmic preparations such as Dexafree®.

Cushing's syndrome and/or adrenal suppression associated with the systemic absorption of ophthalmic dexamethasone may occur after long-term or intensive continuous treatment in sensitive patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and cobicistat). In this case, treatment should be discontinued gradually.

Visual disturbances may occur with systemic or local corticosteroid therapy. If blurred vision or any other visual symptoms occur during corticosteroid therapy, an ophthalmological examination is required to check for cataract, glaucoma, or a rarer lesion such as central serous chorioretinopathy, which has been described with systemic or local administration of corticosteroids.

Posterior subcapsular cataracts may occur with certain cumulative doses of dexamethasone.

People with diabetes are predisposed to developing these subcapsular cataracts after the topical administration of corticosteroids.

Topical corticosteroids are only recommended for severe forms of allergic conjunctivitis that do not respond to standard treatment and only for a short period of time.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy
There is insufficient data on the use of DEXAFREE® 1 mg/ml single-dose ophthalmic solution during pregnancy to assess potential side effects. Corticosteroids cross the placenta. Teratogenic effects have been observed in animals (see section 5.3). However, there is currently no evidence that teratogenic effects are induced in humans. Effects on the foetus/newborn have been reported (intrauterine growth retardation, inhibition of adrenal cortical function) after the generalised administration of corticosteroids at higher doses. However, these effects have not been reported in ophthalmic use.
As a precautionary measure, **it is preferable to avoid the use of DEXAFREE® 1 mg/ml eye drops solution in single-dose containers during pregnancy.**

Breastfeeding
It is not known whether this drug is excreted in breast milk. However, the total dose of dexamethasone is low. DEXAFREE® 1 mg/ml eye drops solution in single-dose containers **can be used during breastfeeding.**

Fertility
There is no information regarding the potential effect of dexamethasone 1 mg/ml on fertility.

SIDE EFFECTS

Very common (≥1/10): Increased intraocular pressure (after 2 weeks of treatment).
Common (≥1/100 to <1/10): Discomfort, irritation, burning, tingling, itching and blurred vision.

For more information on uncommon or rare side effects, please refer to the SmPC.
Report any suspected drug side effects immediately to your Regional Pharmacovigilance Centre (CRPV) or at www.signalement-sante.gouv.fr.

List I – Soc Sec Reimbursement 65% Coll Accredited

See the Summary of Product Characteristics on the Public Drug Database for complete information by scanning this QR Code or by going directly to the website: http://base–donnees–publique.medicaments.gouv.fr

SOFTACORT® SAFETY DATA

Hydrocortisone Sodium Phosphate 3.35 mg/ml:
Treatment of moderate and non-infectious conjunctival pathologies with an allergic or inflammatory origin.

CONTRAINDICATIONS

- Hypersensitivity to the active ingredient or to any of the excipients.
- **Known glucocorticoid-related** ocular hypertension and other forms of ocular hypertension.
- **Acute viral corneal infections** (*Herpes simplex* or others) at the ulceration stage, conjunctivitis with ulcerative keratitis at the initial stage.
- **Anyocular infection that may be masked or aggravated by the administration of anti-inflammatory drugs**.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- **Local corticosteroids should never be used in the presence of un-diagnosed red eye**.
- This medicinal product is **not recommended for the treatment of herpetic keratitis**, but may only be used, if necessary, in combination with an antiviral treatment and under the close supervision of an ophthalmologist.
- Pathological **thinning of the cornea and sclera** may increase the risk of perforation when using local corticosteroids.
- A fungal infection should be suspected if corneal ulceration occurs when a corticosteroid is or has been used for an extended period of time.
- **Patients treated with hydrocortisone eye drops should be monitored frequently**.
- Prolonged **use of** corticosteroids may cause **ocular hypertension or glaucoma**, particularly in patients with a history of corticosteroid-induced IOP elevation or with pre-existing elevated IOP or glaucoma, and the development of **cataracts**, especially **in children and the elderly**.
- The use of corticosteroids can lead to **opportunistic eye infections** due to the suppression of the host response or delayed healing. In addition, local corticosteroids administered ophthalmically may enhance, aggravate or mask the signs and symptoms of opportunistic ocular infections.
- Contact lenses should not be worn during treatment with eye drops that contain corticosteroids.
- **Visual impairments may occur with systemic or local corticosteroid therapy**. In the event of blurred **vision or any other visual symptoms appearing during corticosteroid therapy administration, an ophthalmological examination is required** to investigate cataracts, glaucoma, or a rarer lesion such as a central serous chorioretinopathy, which has been described with the systemic or local administration of corticosteroids.

In children
- Long-term **continuous treatment with** corticosteroids can cause **adrenal insufficiency.**
- **Ocular hypertension associated with the use of topical corticosteroids is more frequent, more severe and more rapid than that reported in adults.**

PREGNANCY AND BREASTFEEDING

Pregnancy
The use of SOFTACORT® is not recommended during pregnancy unless absolutely necessary.

Breastfeeding
Glucocorticoids administered systemically are excreted in breast milk and may cause stunted growth or endogenous corticoid production or may have other side effects. It is not known whether SOFTACORT® is excreted in breast milk. **A risk to neonates/infants cannot be ruled out.**

SIDE EFFECTS

No very common or common side effects have been reported.

Please refer to the SmPC for more information on uncommon or rare side effects.
Report any suspected drug side effects immediately to your Regional Pharmacovigilance Center (CRPV) or at www.signalement-sante.gouv.fr.

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