





Antiinflammatory treatment

<p>We recommend the use of topical corticosteroids (TCS) as anti-inflammatory agents.</p>	<p>↑↑</p>	<p>>75%</p>  <p>(24/26) Expert Consensus</p>
<p>We recommend the use of topical calcineurin inhibitors (TCI) as anti-inflammatory agents.</p>		
<p>We suggest using anti-inflammatory topical agents according to the fingertip unit rule.</p>	<p>↑</p>	<p>>75%</p>  <p>(23/26) Expert Consensus</p>
<p>We suggest the use of wet wraps with diluted (see background text) or low potency topical corticosteroid in acute AE.</p>	<p>↑</p>	<p>>50%</p>  <p>(14/22) Expert Consensus</p>
<p>We recommend TCS in AE especially for treatment of acute flares.</p>	<p>↑↑</p>	<p>100%</p>  <p>100 % Agreement</p> <p>(23/23) Expert Consensus</p>
<p>We recommend to note and adequately address patients concerns or fears about corticosteroid side effects.</p>		
<p>We recommend using TCI particularly in skin areas with a risk of skin atrophy due to TCS application (face, intertriginous sites, anogenital area).</p>		

<p>We suggest initial treatment with topical corticosteroids before switching to a TCI to reduce the risk of skin stinging and burning.</p>	↑	<p style="text-align: center;">100%</p> <p style="text-align: center;">100 % Agreement</p> <p style="text-align: center;">(23/23) Expert Consensus</p>
<p>We recommend proactive therapy (e.g. twice weekly application) with a suitable TCS or a suitable TCI (see background text) to reduce the risk of relapse and for better disease control.</p>	↑↑	<p style="text-align: center;">100%</p> <p style="text-align: center;">100 % Agreement</p> <p style="text-align: center;">(22/22) Expert Consensus</p>

Effective topical therapy depends on three fundamental principles: sufficient potency, sufficient dosage and correct application.¹ Current approved topical anti-inflammatory therapies are corticosteroids (TCS), calcineurin inhibitors (TCI) and a phosphodiesterase 4 (PDE-4) inhibitor, which is approved in the European Union but not yet available.

Aim of this chapter was to give an overview of the efficacy and safety profile of the current topical therapies and provide a summary of emerging topical treatments for AE.

Based on a systematic search in common databases we conducted a revision of the existing consensus papers.

The applied amount of anti-inflammatory topicals should follow the fingertip unit rule (see chapter emollient therapy). Topical treatment should ideally be applied on hydrated skin, especially when using ointments ('soak and seal' approach).

Topical anti-inflammatory therapy can be done by two approaches: reactive and proactive management. In the reactive treatment regimen, anti-inflammatory topical therapy is applied to lesional skin only and is stopped or rapidly tapered, once visible lesions are cleared or almost cleared. The proactive therapy is defined as a combination of predefined, long-term, anti-inflammatory treatment applied usually twice a week to previously affected areas of skin in combination with liberal daily use of emollients on the entire body. Additionally, it is marked by a predefined appointment schedule for clinical examinations.² The proactive regimen is started after the therapy of the acute flare, when lesions have been successfully treated with regular anti-inflammatory therapy. The duration of the proactive management is usually adapted to the severity and persistence of the disease.³

Patients with acute, erosive and oozing lesions as well as paediatric patients sometimes do not tolerate standard topical application and may first be treated with 'wet wraps' until the oozing stops. Where clinically superinfected skin is suspected, adding oral antibiotic cover should be considered. Wet wrap medications are highly effective in acute AE and improve tolerance. The use of wet-wrap dressings with diluted or lower potency corticosteroids (group II, III, typical dilutions used are 1:3-1:10, usually just for a few days is sufficient) are a safe crisis intervention treatment of severe and/or refractory flares of AE with temporary systemic bioactivity of the corticosteroids as the only reported serious side effects.⁴⁻⁷ Wet wraps can be conducted with topical corticosteroid creams and ointments.⁸ However,

this treatment approach is not standardized yet, and the evidence that it is more effective than conventional treatment with topical corticosteroids in AE is not of high quality. Simple or occlusive medications in less sensitive skin areas and for brief time periods may also increase efficacy and speed up lesion resolution.

Topical corticosteroids

Mechanisms of action and efficacy

Topical corticosteroids (TCS) are a first-line anti-inflammatory treatment, typically applied on acutely inflamed skin according to the needs (pruritus, sleeplessness, new flare).^{9, 10} The lipophilicity and the low molecular weight of TCS allows good penetration into the skin and binding to a steroid receptor in the cytoplasm. The CS-receptor complex acts as a transcription factor with dual activity decreasing the synthesis of proinflammatory cytokines and increasing the synthesis of anti-inflammatory mediators. The potency of topical corticosteroids is grouped according to Niedner from mild (class I) to super-potent (class IV).¹¹ This classification is used across Europe, except for France, where this classification is similar but in an inversed ranking. This classification is used throughout this guideline. In contrast, the US-American classification differs and recognises 7 groups: from VII (weakest) to I (most potent).

Latest generation TCS with a better risk-benefit ratio are favoured over earlier generation TCS.

Dosage: acute flare, short term, long term

When choosing a TCS beside potency the galenic formulation, patient age and body area to which the medication will be applied should be considered. In children, low to moderate potency TCS should routinely be used. Adolescent and adult patients can use potent to very potent TCS under specialist supervision in an acute flare of AE for a short period of time. Potent and very potent TCS are sometimes also used in younger age groups under specialist supervision.

Treatment of the face and especially the peri-orbital region or other sensitive areas (folds, neck) should be restricted to mild-to-moderate TCS (class I and II).¹²

With mild disease activity a small amount of TCS twice to thrice weekly (monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60–90 g in adolescents and adults, roughly adapted to affected body surface area), associated with a liberal use of daily emollients allows for a good weekly maintenance treatment routine.

Also, patients with moderate or severe AE can benefit from long-term proactive treatment with a moderate to potent TCS. Twice weekly application of fluticasone propionate or methylprednisolone aceponate (TCS class III) has shown a significantly reduction of AE-flare recurrence. Outside of the context of clinical trials, similar experience also exists for other class III and even class II TCS.^{9, 10, 13}

Safety

Potent and very potent TCS of group III and IV may be absorbed systemically and can more likely cause depression of adrenal function than group I and II treatments, but their systemic effects will decrease more quickly due to more rapid restitution of the skin barrier, and cases of significant adrenal suppression from long-term TCS use are very rare.¹⁴ Ghajar et al. reviewed 9 studies (n=371) measuring serum cortisol levels after two weeks of TCS application. Low to moderate potency TCS showed no risk for adrenal suppression after short-term use.¹⁵ Fishbein et al. reviewed 12 studies with 2224 children using TCS. In 4 of 157 measured participants (3%) mild adrenal suppression was reported.¹⁶

Side-effects of TCS comprise a variety of skin changes mostly in the sense of skin atrophy – except from contact allergy to corticosteroid substances. The skin changes manifest as thinning of the skin, development of teleangiectasia (rubeosis steroidea), spontaneous scars (pseudo-cicatrices stellatae), ecchymosis, striae distensae (stretch marks) and hypertrichosis.¹⁷

A review of 11 trials showed a prevalence rate of burning, pruritus, irritation or warmth after TCS application ranging from <1% to 6%.¹⁸

In infants, inappropriate use of high potency TCS in the diaper area can lead to granuloma gluteale infantum or even iatrogenic Cushing's disease.¹⁹

The risk of ocular complications by TCS seems to be low. The application of TCS to the eyelids and periorbital region in adults with AE, even over longer periods of time, was not associated to the development of glaucoma or cataracts.²⁰ However, there are single case reports of increased intraocular pressure after topical application of TCS, therefore physicians should be aware of this potential risk.^{21, 22}

In the face, rosacea-like perioral dermatitis can be induced by inappropriate, long term use of potent or super-potent TCS (group III, IV) and the skin can become dependent on TCS use ("red face syndrome" or "corticosteroid addiction syndrome"). It is characterized by persistent erythema, burning and stinging sensation and it has been reported mostly on the face and genital area of women.²³

Monitoring

Monitoring by physical examination for cutaneous side effects during long term use of potent TCS is very important.

Itch, which can be assessed by itch Numeric Rating Scale (NRS), is the key symptom for evaluation of response to treatment, and tapering should not be initiated before the itch has largely resolved. In addition to continuous background emollient skin care, one to two applications of TCS per day may be necessary with low and mid-potency TCS to reduce the itch at the beginning, but one correctly dosed treatment per day is typically sufficient.^{24, 25} Dose tapering is usually performed to avoid rebound flares, although no controlled studies have demonstrated its usefulness. Tapering strategies consist of switching to a less potent corticosteroid or keeping a more potent one while reducing the frequency of application (intermittent regimen). The most constructive way to spare corticosteroids and avoid corticosteroid-related side-effects is to start the anti-inflammatory treatment early and use them intensively during the acute flares.¹

Combination with other treatments

The combination of TCS with topical calcineurin inhibitors (TCI) at the same site does not seem to be useful. At least in pediatric patients with severe AE, the efficacy and safety profile of pimecrolimus cream 1% combined with fluticasone were similar to that of fluticasone alone.²⁶ Treating sensitive body areas such as the face (with predilection to skin thinning) with TCI while treating other affected body areas with a TCS is a common practice but class I and II TCS can be used equally effectively in the face and neck for acute flares. Initial treatment with TCS may be considered in patients with acute flare to minimize TCI site reactions (stinging and burning).³

Special considerations

Patient fear of side effects of corticosteroids (corticophobia) is quite common and should be recognized (e.g., by TOPICOP score²⁷) and adequately addressed to improve adherence and avoid undertreatment.²⁸⁻³⁰

In pregnancy and lactation lower potency TCS should be used where possible (see chapter Pregnancy, breastfeeding, and family planning).

Topical calcineurin inhibitors

Mechanisms of action and efficacy

Two topical calcineurin inhibitors (TCI) (tacrolimus ointment and pimecrolimus cream) are licensed for AE treatment. Pimecrolimus 1% cream and tacrolimus 0.03% ointment are approved in the EU from 2 years of age and above. Elidel® cream has additionally been approved in Europe down to 3 months of age. Tacrolimus 0.1% ointment is only licensed in patients age 16 years and above. TCIs have an immunosuppressive effect by inhibiting the activity of the phosphorylase enzyme calcineurin and thus inhibiting the activation of T lymphocytes. The transepidermal penetration of TCI is lower than TCS.^{31, 32} TCI are a first line therapy for sensitive areas where TCS use is likely associated with side effects or in areas where TCS had already caused side effects. The efficacy of both formulations has been demonstrated against vehicle in clinical trials for short-term (three weeks)^{33, 34} and long-term use up to one year.^{35, 36}

The efficacy of long-term monotherapy with tacrolimus ointment has been shown in children and adults.³⁷⁻³⁹ In adults, long-term proactive treatment with 0.1% tacrolimus ointment has shown good effectiveness for flare prevention, similar to class III TCS.³⁸ Proactive tacrolimus ointment, but not Pimecrolimus 1% cream, has been shown to be safe and effective for up to 1 year in reducing the number of flares and improving the quality of life (QoL) in both adults and children.^{40, 41} Pimecrolimus 1% cream has been studied in infants and children in a combination regimen with TCS^{42, 43}, the latter being given if a flare occurred. Less data are available for children under 2 years of age.^{44, 45} In children, twice-weekly treatment with tacrolimus 0.03% ointment has been reported to reduce the number of flares and to prolong flare free intervals.

Dosage: acute flare, short term, long term

The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a potent corticosteroid (class III)^{37, 38, 46}, and 0.1% tacrolimus ointment is clearly more effective than 1% pimecrolimus cream.³⁹

TCS and TCI can be used in a daily regimen during an acute AE-flare. The efficacy of intermittent treatment twice or three times weekly has been investigated in different trials.^{40, 41}

Safety

Safety data of both TCI have been reported in many clinical trials and registries and high-quality long-term safety data have been published on 10-year tacrolimus and 5-year pimecrolimus studies, demonstrating the safety of this anti-inflammatory treatment in daily practice.^{47, 48}

None of the TCI induces skin atrophy.^{49, 50} This favors their use over TCS in sensitive body areas such as the eyelid region, the perioral skin, the genital area, the axilla region or the inguinal fold, and makes them suitable for long-term management. In addition, the use of TCI may potentially reverse some of the side effects of TCS when applied on sensitive areas.⁵¹

The most frequently observed side effect is transient warmth, tingling or burning sensation at the application site, which may last up to 1 h.^{26, 38} However, this side effect typically vanishes within a few days.⁵² Some patients also experience a transient worsening of their AE. These side effects are more

common with tacrolimus ointment than with pimecrolimus cream, in particular when they are applied on acutely inflamed skin. In some patients they are severe enough to induce prompt treatment discontinuation. Initial treatment with TCS should thus be considered in patients with an acute flare to minimize these site reactions.³ In some patients intake of alcohol can trigger transient but marked facial flushing, this innocent but annoying side effect is very inconsistent even in the same patient.

Generalized viral infections such as eczema herpeticum or eczema molluscatum have been observed during TCI treatment in some studies^{53, 54}, but a high number of clinical trials failed to demonstrate an increased frequency or showed only a transient increase in viral infection.^{53, 55-57}

After initial concerns from animal studies, resulting in a black box warning from the US Food and Drug Administration (FDA), no convincing evidence for an increased risk of lymphoma has been found in humans.⁵⁸ A long-term safety study over 10 years using tacrolimus ointment 0.03% or 0.1% in children did not show an increased risk of cancer or lymphoma.⁵⁹ The application of TCI is not associated with an increased risk for non-melanoma skin cancer, other malignancies or photocarcinogenicity.^{48, 60-64} In a retrospective cohort study with more than 90,000 participants and over ten years, no increased risk of basal cell carcinoma or squamous cell carcinoma was observed.⁶⁵ The JOELLE study investigated the risk of lymphoma and skin cancers with the use of TCI and TCS in a very large cohort of paediatric and adult patients and found a positive association. However, given the study design, confounding factors, such as disease severity, have not been ruled out.⁶⁶ A recent paediatric prospective observational cohort study (APPLES, n=7,954) found no significant association between regular tacrolimus use and lymphoma risk over a 10 year follow up period. Nevertheless, given that the long-term oral use of cyclosporine (calcineurin inhibitor) is associated with an increased photocarcinogenicity risk in solid organ transplant patients, exposure of the skin to sunlight should be minimized and effective UV protection through the use of sunscreens and appropriate clothing should be recommended in all patients using TCI. Furthermore, the combined use of TCI and phototherapy should be avoided.⁶⁷

Clinicians should be aware of the black-boxed warning on the use of TCI inhibitors and may discuss this with patients to improve adherence, even if the observational study evidence has not found a convincing association between long-term TCI use and cancer development.⁵⁹

Monitoring

Monitoring by physical examination for cutaneous side effects during long term treatment with TCS and TCI is important (also see above).

Special considerations

Though TCIs are not approved in pregnancy and lactation (see chapter Pregnancy, breastfeeding, and family planning), off-label use in pregnancy and lactation is possible as there is no teratogenic potential reported for the entire substance class.⁶⁸

Topical phosphodiesterase 4 inhibitors

Mechanisms of action and efficacy

The topical phosphodiesterase 4 (PDE-4) inhibitor, crisaborole, is approved for treatment of mild to moderate AE in patients 2 years of age and older in the United States of America, Canada, Australia, Israel and Hong Kong. Crisaborole has been approved in the European Union in 2020 but is not commercialized in the European market.

The inhibition of PDE-4 leads to increased levels of intracellular cAMP, which results in a reduction of inflammatory cytokines.^{69, 70} Several studies have reported anti-inflammatory and anti-pruritic effects of crisaborole in AE.^{71, 72} A systematic review by Fahrback et al. with nine randomized controlled trials confirmed the efficacy of crisaborole.⁷³ However, only three studies provided baseline EASI and none provided SCORAD measurement. In the pivotal studies, efficacy was only assessed by Investigator Static Global Assessment (ISGA).⁷⁴ Therefore, a direct comparison of the efficacy of crisaborole against TCI or TCS is currently not possible. Based on available data the efficacy of PDE-4-inhibitors seems to be similar to mild TCS or pimecrolimus, however further studies are needed.

Safety

Reported side-effects of crisaborole were short-term application-site pain, burning or stinging.⁷⁴ Also the long-term safety profile over 48 weeks appears to be favorable.⁷⁵

Special considerations

Other topical phosphodiesterase 4 inhibitors under investigation include Lotamilast (RVT-501) and Difamilast (OPA-15406).⁷⁶⁻⁷⁸

Upcoming topical treatment

Upcoming topical therapies include several topical janus-kinase (JAK) inhibitors. First promising phase II clinical trial data with the topical JAK-inhibitor tofacitinib have been published.⁷⁹ Despite these promising results, the clinical development programme of tofacitinib has been stopped. Delgocitinib has been approved for the use in AE in Japan.^{79, 80} In a 4-week study the selective JAK-1 and JAK-2 inhibitor ruxolitinib showed a similar or even higher efficacy in mild to moderate AE compared to triamcinolone cream (group III TCS), and has recently been approved in the US.⁸¹ Other JAK inhibitors with similar or different selectivity (brepocitinib) are in the pipeline for topical therapy, but none is currently licensed in Europe.

Further upcoming therapies include tapinarof, an aryl hydrocarbon receptor agonist, which showed greater efficacy in AE treatment than vehicle twice daily after 12 weeks.⁸²

The transient receptor potential vanilloid 1 (TRPV1) antagonist, PAC-14028, was investigated in a phase IIb study in patients with mild to moderate AE and showed a significantly higher reduction in IGA than vehicle cream. Although there was an improvement in AE according to SCORAD and EASI, the effects of PAC-14028 were not statistically significant compared to the vehicle.⁸³

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