Topical Calcineurin Inhibitors

Topical Calcineurin Inhibitors – Primary Care Treatment Pathway

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PCDS PRIMARY CARE DERMATOLOGY SOCIETY

What Are Topical Calcineurin Inhibitors?

- Topical calcineurin inhibitors (TCIs) are a class of steroid-free anti-inflammatory topical treatments used for the treatment of many inflammatory skin diseases such as eczema
- They work as **immunomodulators** by inhibiting calcineurin and pro-inflammatory cytokines in the skin
- **They work differently to topical corticosteroids (TCS) and are steroid-sparing**: they do not cause the skin thinning, striae, nor ocular disease associated with prolonged or inappropriate TCS use
- They are particularly useful for the longer-term maintenance treatment, and for treating delicate areas such as the eyelids, face, and flexures

What TCIs Are Available And How Do I Choose?

- TCIs are available as either a **cream** (pimecrolimus, *Elidel*®), or an **ointment** (Tacrolimus 0.03% and 0.1%, *Protopic*® 0.03% & 0.1%)
- Pimecrolimus is licensed for use from 3 months of age, onwards
- Tacrolimus 0.03% is licensed for 2 years and up, and tacrolimus 0.1% from age 16 and up
- Most Dermatology specialists will use **tacrolimus 0.1% off-license in under 16 years of age**, where appropriate, as this is more **superior to and more efficacious than 0.03%** especially in eczema and vitiligo; this is advocated in the PCDS paediatric eczema treatment pathway
- In general, benefit in clinical effect increases from pimecrolimus to tacrolimus 0.03% to 0.1%
- Due to differences in how potency is measured, a like-for-like comparison of TCS and TCI is challenging. Approximately, pimecrolimus and tacrolimus 0.03% would be suitable for low-moderate severity inflammation (comparable to a mild and moderate potency TCS, respectively) and tacrolimus 0.1% for moderate-severe (comparable to a potent TCS)
- Treatment choice depends on age, vehicle preference, and desired efficacy

What Conditions Can I Use TCIs For?

- TCIs are **excellent** for the management of many skin diseases
- Their **main use is in the management of eczema**
- Off-license, supported by routine, established practice and/or guidelines, they are used in psoriasis, seborrheic dermatitis, vitiligo, hand dermatitis, **as well as for many other dermatoses**

Can I Prescribe TCIs?

- **Many national and international guidelines support the use of TCIs, where appropriate, and do not limit TCI initiation to specialists only**
- The advice provided by the British National Formulary (BNF) regarding the initiation of TCI therapy requires immediate revision, which impedes the widespread use of this valuable class of medications in primary care.
- The summary of product characteristics (SmPC) for both tacrolimus and pimecrolimus state that “treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis”: this will include those in primary care who assess and start treatment of eczema

Frequent Questions

- **Who can prescribe TCIs?** Any Primary Care practitioner who assesses and initiates treatment for skin disease in children and adults
- **Will TCIs cause cancer?** TCIs are **safe and effective** treatments, and accumulated evidence in **all age groups** has **not shown any increased risk** of developing cancers
- **What should I do if my formulary shows a warning when I try to prescribe?** Please discuss with your local medicines management to update their guidance. Signpost them to this resource and the PCDS website!

How Are TCIs Applied?

- TCIs are generally applied **twice daily**, thinly (enough to leave the skin glistening)
- When used for maintenance, apply once a day, twice a week (e.g. Monday & Friday or Saturday & Sunday)
- **Apply emollient after**, if part of treatment
- **Review in 4 weeks**. If no better, re-consider the diagnosis, or consider referral or advice & guidance depending on local provision
- Do NOT use TCIs under occlusive dressings unless advised by secondary care
- Stop / interrupt TCIs if skin becomes infected (e.g. Infected eczema, impetigo or herpes simplex). Recommence when the infection has resolved

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License And Safety Concerns

- **Lymphoma. No evidence of increased risk of lymphoma has been found** in 25+ years of use in paediatric or adult patients with TCIs
- **Skin cancer.** Systemic immunosuppressants including oral calcineurin inhibitors are associated with increased risks of skin cancer; TCIs have **not been associated with this risk**, but safe sun exposure should be practiced by all.
- **Pregnancy.** Use in pregnancy is off-license. From registry information and worldwide experience, oral calcineurin inhibitors have not shown to adversely affect pregnancy. Systemic absorption of TCIs is low; **use in pregnancy is recommended by international guidelines**. As always, a balanced discussion must be made with the individual patient sharing all risks and benefits
- **Lactation.** Use during breast-feeding is off-license. Practical advice would be that TCIs are applied after breast-feeding, if needed, on the nipples, but gently clean the nipples before the next feed, to ensure that no trace remains. If applied to skin not in contact with the infant, and given that system absorption of TCIs is low, harm is unlikely to occur. **Use in lactation is supported by international guidelines**, but a balanced discussion must be made with the individual patient sharing all risks and benefits
- **Use around genitals:** Numerous guidelines do support the use of TCIs in genital disease but **caution must be exercised in uncircumcised males** especially in the presence of penile lichen sclerosus (DOI: 10.1001/archderm.140.9.1169-a and 10.1111/jdv.18954). Seek secondary care advice if unsure
- **Other precautions:** Avoid use, without secondary care guidance, of TCIs in patients where increased absorption may occur, such as in Netherton syndrome, lamellar ichthyosis, generalized erythroderma

Tips And Tricks For Using TCIs

- If skin is acutely inflamed, TCIs are more likely to sting. **Put out the fire** with a short course of moderately potent or potent TCS (as appropriate) for 5-7 days
- Start TCI application, twice daily, to affected skin to **get it good** (not inflamed, not itchy, skin feels normal)
- Once settled, use TCIs twice a week, once daily, as maintenance to **keep it good**
- If the skin becomes 'bad', go back to getting it good, then resume maintenance treatment
- Using the '**get it good, keep it good**' regime has been shown to decrease flare frequency and intensity and overall TCS use

Side Effects And How To Manage

- **Stinging**. This is a **common** (1 in 10) effect of TCI use and manifests as stinging or discomfort within 5 minutes of application to the skin. It last several hours. **It is not a sign of harm** and indeed is a positive and expected effect of treatment. Perseverance and continued used usually results in the skin tolerating application within 1-2 weeks, and discomfort abates completely. See 'Tips and Tricks' above on calming any acute inflammation down first. TCIs can be cooled, 10-15 minutes before application, in the fridge, and then applied to skin. This will sting less. If stinging persists, trial a less potent TCI or change from ointment to cream (or vice versa), and apply moisturizer immediately after. Finally, ensure, it is being applied thinly
- **Flushing with alcohol**. This is a common side effect and results in flushing if alcohol consumed after TCI application. This may last several hours. This is not a harmful side effect, but may be uncomfortable
- **Infections**. Whilst TCIs do not cause infections, they should not be used where active herpes simplex virus (e.g. eczema herpeticum) or impetigo is present

When To Seek Help

- If, despite prolonged use (4 weeks), there is no effect
- If side effects, including application site burning means patient cannot tolerate TCIs
- If the patient develops a local skin infection, herpes simplex, eczema herpeticum or folliculitis, TCIs should be discontinued until infection has resolved

Other Resources

- Please note this is a moving field, and do consider that some information on websites may be out-of-date and need refreshing.
- PCDS website (TCI chapter in A-Z guidance with references provided)
- BAD TCI PIL
- National Eczema Society website (TCI factsheet)
- Eczema Care Online website