SHARED CARE GUIDELINES FOR PRESCRIBING TACROLIMUS (PROTOPIC®) FOR TREATMENT OF MODERATE TO SEVERE ATOPIC ECZEMA IN ADULTS AND CHILDREN

INDICATION

Topical tacrolimus is recommended as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged 2 years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of tacrolimus can be shared between the specialist and general practitioner (GP). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION

Shared Care is only appropriate if it provides the optimum solution for the patient.

Patients will only be referred to the GP once the GP has agreed in each individual case.

Guidance regarding the use of tacrolimus has been included in the NICE technology appraisal 'tacrolimus and pimecrolimus for atopic eczema' (**TA82**). The specific guidance regarding tacrolimus is:

Topical tacrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged 2 years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.

Atopic eczema that has not been controlled by topical corticosteroid refers to disease that has not shown a satisfactory clinical response to adequate use of the maximum strength and potency that is appropriate for the patient's age and the area being treated.

The NICE Clinical Guideline 'Atopic eczema in children', (CG57), also states:

Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity. It is recommended that treatment with tacrolimus or pimecrolimus be initiated only by physicians (including general practitioners) with a special interest and experience in dermatology, and only after careful discussion with the patient about the potential risks and benefits of all appropriate second line treatment options.

Healthcare professionals should explain to children with atopic eczema and their parents or carers that they should only apply topical calcineurin inhibitors to areas of active atopic eczema, which may include areas of broken skin.

Specialist Responsibilities	
1	To assess the patient and establish the diagnosis, determine a management strategy and ensure appropriate follow-up in conjunction with the GP.
2	Where appropriate: o to initiate treatment; o assess initial response to treatment after 6 weeks and assess benefit from treatment, including changes to strength of ointment required o obtain consent from the patient's GP to continue prescribing once treatment has been stabilised (usually after 6-8 weeks); o monitor the patient and their therapy at six monthly intervals.
3	Ensure that the patient or carer understands the management of the condition. In the long term management of atopic eczema, treatment should begin at first appearance of signs and symptoms of atopic dermatitis to prevent flares of the disease and should be stopped when those signs and symptoms have resolved
4	To provide the GP with appropriate prescribing information and any additional information requested.
5	To be available for advice if the patient's condition changes.
6	To ensure that procedures are in place for the rapid re-referral of the patient by the GP.
7	To ensure the patient has given informed consent to their treatment.
8	To liaise with the GP on any suggested changes in prescribed therapy.

General Practitioner Responsibilities	
1	Initially, to refer the patient for specialist advice.
2	Where appropriate, to continue to prescribe tacrolimus as part of a shared care arrangement (usually after 6-8 weeks).
4	To deal with general health issues of the patient.
5	To advise the patient/carer of appropriate sun protection measures, such as minimisation of the time in the sun, use of sunscreen product and covering the skin with appropriate clothing.
6	To monitor concordance with therapy

Responsibility of community pharmacies	
1	To provide support and advice to the patient and/or family regarding concordance, adverse effects and over the counter therapies.
2	To advise the patient/carer about appropriate sunscreen products.
3	To monitor concordance with therapy and refer the patient to their GP if any concern arises.

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Attend appropriate GP and other follow up appointments
3	Share any concerns in relation to treatment with tacrolimus
4	Use written and other information on the medication.
5	Seek help urgently if side effects are suspected, or if otherwise unwell.

SUPPORTING INFORMATION

Dosage and Administration

Topical tacrolimus (Protopic ®) is available in two strengths, 0.03 % and 0.1 % ointment. Tacrolimus can be used for short-term and intermittent long-term treatment. Treatment should **not** be continuous on a long-term basis.

Tacrolimus treatment should begin at the first appearance of signs and symptoms. Each affected region of the skin should be treated with tacrolimus until lesions are cleared, almost cleared or mildly affected. Thereafter, patients are considered suitable for maintenance treatment (see below). At the first signs of recurrence (flares) of the disease symptoms, treatment should be re-initiated.

TREATMENT OF FLARES

Adults and adolescents (16 years of age and above)
Treatment should be started with tacrolimus 0.1% twice a day and treatment should be continued until the lesions are cleared, almost cleared or mildly affected, treatment should be reduced to use of the 0.1% ointment once daily **OR** switch to twice daily use of the lower strength (0.03%) ointment. If symptoms recur, twice daily treatment with the 0.1% ointment should be restarted. Generally, improvement is seen within one week of starting treatment.

Children (age of 2 to 16 years).
Tacrolimus 0.03% ointment should be applied to affected skin twice daily for up to three weeks until the lesions are cleared, almost cleared or mildly affected, then treatment should be reduced to use of the 0.03% ointment once daily. The higher strength tacrolimus ointment (0.1%) is not suitable for use in children.

In adults and children, if no signs of improvement are seen after two weeks of treatment, other treatment options should be considered.

MAINTENANCE TREATMENT

Patients who are responding to treatment with tacrolimus ointment (lesions cleared, almost cleared or mildly affected) are suitable for maintenance treatment.

Adults and adolescents (16 years of age and above)
Adult patients should apply tacrolimus 0.1% ointment once a day twice a week to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2–3 days without tacrolimus treatment (e.g. apply ointment on Monday and Thursday each week).

During maintenance treatment, patients should be monitored for response to therapy and the need for continued treatment should be evaluated. After 12 months treatment, a review of the patient`s condition should be conducted by the consultant and a decision taken whether to continue maintenance treatment in the absence of safety data for maintenance treatment beyond 12 months.

Children (age of 2 to 16 years).
Tacrolimus 0.03% ointment should be applied to affected skin twice a week to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2–3 days without tacrolimus treatment (e.g. apply ointment on Monday and Thursday each week). The higher strength tacrolimus ointment (0.1%) is not suitable for use in children.

During maintenance treatment, patients should be monitored for response to therapy and the need for continued treatment should be evaluated. After 12 months treatment, a review of the patient`s condition should be conducted by the physician and a decision taken whether to continue maintenance treatment in the absence of safety data for maintenance treatment beyond 12 months.

Method of administration

Tacrolimus ointment should be applied as a thin layer to affected areas of the skin and rubbed in gently. Tacrolimus ointment may be used on any part of the body, including face, neck and flexure areas, except on mucous membranes. Tacrolimus ointment should not be applied under occlusion (dressings and bandages).

Emollients should **not** be applied to the same area within 2 hours of applying tacrolimus ointment.

Contraindications

Tacrolimus ointment is contraindicated:

- in patients with a known hypersensitivity to the drug, other macrolactams or any of the excipients
- in pregnant or breastfeeding women

Special Warnings

Tacrolimus ointment should not be used in:

- congenital or acquired immunodeficiencies
- patients on therapies that cause immunosuppression.
- potentially malignant or pre-malignant skin lesions.
- clinical infections at treatment sites
- patients requiring occlusive dressings
- patients with Netherton's syndrome, lamellar ichthyosis, generalized erythroderma or cutaneous Graft Versus Host Disease.

Treatment with tacrolimus may be associated with an increased risk of folliculitis and herpes viral infections (herpes simplex dermatitis, herpes simplex, Kaposi's varicelliform eruption). In the presence of these infections, the balance of risks and benefits associated with tacrolimus use should be evaluated.

Tacrolimus is extensively metabolised in the liver and although blood concentrations are low following topical therapy, the ointment should be used with caution in patients with hepatic failure.

Care should be exercised if applying tacrolimus to patients with extensive skin involvement over an extended period of time, especially in children.

Patients with severe atopic dermatitis may have an increased risk of skin bacterial infections (e.g. impetigo) during treatment with tacrolimus ointment.

Care should be taken to avoid contact with eyes and mucous membranes. If accidentally applied to these areas, the ointment should be thoroughly wiped off and/or rinsed off with water. As with any topical medicinal product, patients should wash their hands after application if the hands are not intended for treatment.

Physicians should advise patients on appropriate sun protection measures, such as minimisation of the time in the sun, use of sunscreen product and covering the skin with appropriate clothing. The use of ultraviolet (UV) light from a solarium, therapy with UVB or UVA in combination with psoralens (PUVA) should be avoided during use of tacrolimus ointment.

Cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers have been reported in patients using tacrolimus ointment. However, patients with atopic dermatitis treated with tacrolimus ointment have not been found to have significant systemic tacrolimus levels.

Lymphadenopathy present at initiation should be investigated and kept under review. Patients who receive tacrolimus ointment and who develop lymphadenopathy should be monitored to ensure that it resolves. In case of persistent lymphadenopathy, aetiology needs to be investigated. In the absence of a clear aetiology or in the presence of acute infectious mononucleosis, discontinuation of Tacrolimus ointment should be considered.

Side Effects

The most common adverse effects are: application-site reactions including rash, irritation, pain and paraesthesia; herpes simplex infection, Kaposi's varicelliform eruption; application-site infections and alcohol intolerance. Less common side effects include acne; also reported rosacea. Post marketing cases of malignancy, including cutaneous and other types of lymphoma and skin cancers have been reported in patients using tacrolimus ointment.

The summary of product characteristics should be consulted for full information with respect to adverse effects and drug interactions.

Drug Interactions

Systemically available tacrolimus is metabolised via the hepatic Cytochrome P450 3A4 (CYP3A4). Systemic exposure from topical application of tacrolimus ointment is low (< 1.0 ng/ml) and is unlikely to be affected by concomitant use of substances known to be inhibitors of CYP3A4. However, the possibility of interactions cannot be ruled out and the concomitant systemic administration of known CYP3A4 inhibitors (e.g. erythromycin, itraconazole, ketoconazole and diltiazem) in patients with widespread and/or erythrodermic disease should be done with caution.

There is no experience with concomitant use of immunosuppressive therapies given for atopic eczema such as UVB, UVA, PUVA. Excessive exposure of the skin to ultraviolet light including light from a solarium, or therapy with PUVA, UVA or UVB should be avoided during treatment with tacrolimus ointment.

The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

References

1. Protopic® (Astellas) Summary of Product Characteristics (January 2013).
2. BNF 64 (September 2012)

Current prices of Protopic ® (tacrolimus ointment):

- 0.1% strength – 30g - £21.60
- 0.1% strength – 60g - £39.40
- 0.03% strength – 30g - £19.44
- 0.03% strength – 60g - £35.46

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