**Issues in Emerging Health Technologies**

**Tacrolimus Ointment for the Treatment of Atopic Dermatitis**

### Summary

- **Atopic dermatitis (AD)** is a chronic dermatological condition characterized by pruritus (itchiness) and rash. Topical corticosteroids are the mainstay of pharmacotherapy.

- **Tacrolimus ointment** is a new topical anti-inflammatory agent available in Canada through the Special Access Program.

- It is approved as a second line agent for short or long term intermittent treatment of moderate to severe AD.

- Clinical trials suggest it is both effective and safe, but comparative studies with corticosteroids and long-term information are limited.

### The Technology

Tacrolimus (FK-506) is a macrolide immunosuppressive agent discovered in 1984 by Japanese researchers who extracted the compound from a soil fungus from Mount Tsukabe in Japan, *Streptomyces tsukubaensis*.1-3

Tacrolimus is currently used systemically to prevent the rejection of transplanted organs and to treat refractory dermatological conditions such as psoriasis.2 However, concerns about systemic side effects (e.g. nephrotoxicity, hypertension) limit its use in dermatology.3 Oral cyclosporin (CsA), another macrolide immunosuppressive agent, is also used in dermatology but is limited by similar adverse effects.5 4 The topical administration of these agents has been investigated to reduce systemic exposure. It was found that topical CsA lacks activity, whereas topical tacrolimus is associated with better clinical effects partially due to better skin penetration.3,5

**Tacrolimus ointment** is a topical immunosuppressive agent.6 It suppresses the early stages of T-lymphocyte activation, impairs the release of mediators from the skin mast cells, and reduces the expression of high affinity receptors for IgE on Langerhans cells.1,5,6

Preliminary information suggests that topical tacrolimus may be useful in other inflammatory skin conditions: pyoderma gangrenosum,2 alopecia areata,4 erosive mucosal lichen planus,7 ichthyosis linearis circumflexa,7 refractory oral and perioral Crohn's disease.7 Both negative11 and positive12,13 results have been reported for psoriasis.

### Regulatory Status

Health Canada has recently granted a notice of compliance (NOC) to the Canadian manufacturer Fujisawa Canada, Inc. (Markham, ON).14 Tacrolimus ointment is currently available through the Special Access Program as a second line agent for the treatment of AD and is expected to reach the Canadian market in the fall of 2001. It was also approved by the regulatory agencies in both Japan (December, 1999)15 and the USA (December, 2000)16 for AD.

### Patient Group

AD (synonymous of atopic eczema) is a chronic skin inflammatory condition.17 It affects 5% to 20% of children worldwide.17 Prevalence in Canada is 8.5% for children at ages 6 to 7 yr and 9.4% for adolescents at ages 13 to 14 yr.17 About 4.7% of young adults in industrialized countries are affected by this condition.2 The frequency of AD has increased during the past three decades from 3% to 10%.18

Symptoms may range from mild skin irritation to a widespread and painful rash.19 Although AD is not a life threatening condition, severe cases may be associated with significant morbidity, including constant scratching, leading to skin damage and secondary infections.17 AD is associated with significant stress on the family, including disturbed sleep for children and parents, reduced employment for parents and financial costs.20
Current Treatments

The treatment of AD incorporates preventive measures and pharmacotherapy. Preventive measures include the recognition and avoidance of common irritants such as certain clothing or soaps. Pharmacotherapy includes the use of agents such as emollients, topical corticosteroids and antibiotics. Topical corticosteroids have been used in the treatment of AD for over 40 years because of their anti-inflammatory properties. Low potency agents are recommended for maintenance therapy while higher potency derivatives are used to treat flare-ups. Local adverse effects from topical corticosteroids include the development of stretch marks and atrophy (thinning) of the skin. Systemic side effects (e.g. adrenal suppression) are considered more serious but their risk may be reduced by alternating topical corticosteroids with “drug holiday” periods using emollients. Antibiotics are used both topically and orally to reduce secondary infections and consequent pruritus. Oral antiviral agents may also be required. Other agents include antihistamines and topical coal tar preparations, although the latter has been associated with low patient acceptance. Psychological support is required because of the social intolerance towards contact with persons affected by AD.

In patients with refractory AD, short courses of systemic corticosteroids may be used. Ultraviolet (UV) light therapy can be a helpful adjunct in the treatment of chronic, persistent AD. Photochemotherapy may be used in patients with severe AD, although long-term side effects include cutaneous malignancies. Oral CsA can be beneficial in selected cases.

Dosage and Potential Costs

Tacrolimus ointment is available under the trade name Protopic in two strengths (0.1% and 0.03%) and sizes (30g and 60g). Both preparations are approved for use in adults, but only the 0.03% formulation is approved for pediatric use (age 2 - 15 yr). A local application of a thin layer on the skin twice daily is recommended. For the launch of the product in the fall, 2001, the Canadian manufacturer quotes prices between $64.55 and $138.00, depending on the strength and the size used.

Projected Rate of Diffusion

Tacrolimus ointment is not a first line agent as it is approved for the short and long term intermittent treatment of patients with moderate to severe AD in whom the use of conventional therapies are deemed inadvisable because of potential risks, or who are not adequately responsive to, or intolerant of, conventional therapies. As a second-line agent, it may be particularly useful for treating corticosteroid-sensitive areas such as the face and neck, as well as for pediatric use.

Concurrent Developments

New treatment modalities in AD are being developed. Interferon derivatives have been used, but appear to be effective only in a subset of patients. Phosphodiesterase inhibitors (e.g. Ro 20-1724, CP-80663) have been shown to have anti-inflammatory effects in AD. A number of derivatives are currently under development. Another topical macrolide derivative, the ascomycin SDZ ASM 981, has demonstrated clinical efficacy in AD and appears to be well tolerated with side effects limited to local burning and stinging at the site of application.

Assessing the Evidence

The first reports assessing topical tacrolimus in the treatment of AD originated from Japan. In their short-term, randomized, clinical trial, Ruzicka et al. reported that three weeks of different concentrations (0.03%, 0.1% and 0.3%) of topically administered tacrolimus ointment, compared to placebo, resulted in a statistically significant decrease in symptoms of dermatitis in 213 adults. Boguniewicz et al. investigated the efficacy and safety of tacrolimus ointment (0.03%, 0.1%, 0.3%), compared to placebo, in 180 children. They reported a significant improvement in dermatitis symptoms. In a short-term open-label study, Aliat et al. investigated the pharmacokinetics, efficacy and safety of tacrolimus 0.3% ointment in 31 adults and eight children. Ninety-five percent of patients reported improvement in their condition. Bioavailability was estimated to be less than 0.5% and less than 5% compared to intravenous and oral administration, respectively. Other short-term (12 weeks) studies in children and adults reported comparable findings. A recent review summarizing the results of early clinical trials published in Japanese reported similar clinical benefits.

In an open-label study evaluating the efficacy and safety of 0.1% tacrolimus ointment in adults, Reitamo et al. followed 200 subjects with moderate to severe AD for six months and 116 for 12 months. Improvement in the areas affected by AD was apparent after one week, and maximal improvement was maintained for the duration of the study. In another open-label study, Kang et al. evaluated the long-term (12 months) safety and efficacy of topical 0.1% tacrolimus ointment in 255 children with moderate to severe disease. Substantial improvement in their condition was reported after one week of therapy. Improvement continued for 12 months in most patients.

Comparative information with corticosteroids is limited. In a small double-blind study comparing 0.1% tacrolimus ointment with hydrocortisone 3% ointment in seven AD patients, Gutgesell et al. reported similar efficacy in six
patients, while tacrolimus was judged to be superior in one patient. Early Japanese clinical trials also reported a mix of comparable efficacy and superior effect for tacrolimus ointment, compared to topical betametasone valerate 0.12% and alclomatasone dipropionate 0.1%. A European clinical trial comparing tacrolimus ointment 0.03% and 0.1% to hydrocortisone butyrate 0.1% ointment in adults is currently underway. A recent evaluation reported significant quality of life benefits associated with the use of tacrolimus ointment in both adults and children.

### Adverse Effects

Current evidence suggests that tacrolimus ointment is safe for both adults and children. Local adverse reactions are mainly limited to a burning sensation and pruritus in the area of application in 0% to 58% of patients. These effects tend to last a few days and usually do not prevent the continuation of treatment. Similar reactions were reported in 4% to 36% of placebo recipients. Tacrolimus ointment is not associated with skin atrophy. An association between tacrolimus ointment and skin infections has recently been suggested, although this observation may simply reflect the predisposition of AD patients for such infections. No remarkable increase in skin infections was reported in the two long-term studies. The whole-blood concentration of tacrolimus remained below 2 ng/ml in most study participants, which would be considered safe as long-term, post-transplant patients are usually maintained at the lower end of the target range of 5-20 ng/ml. Although rodents have a much more permeable skin than man, high dose chronic topical administration of tacrolimus ointment lead to a higher incidence of lymphoma in mice and a decreased time to onset of skin tumor formation in mice exposed to UV radiation. Patients are advised to minimize exposure to natural or artificial sunlight.

### Implementation Issues

Tacrolimus ointment represents an innovative approach for the treatment of AD and there is preliminary evidence supporting its efficacy and safety in both adults and children up to a period of one year. Considering the chronic nature of this condition, additional evaluations are required to better determine the role of tacrolimus ointment in AD, particularly compared to topical corticosteroids, as well as the long-term safety.

### References

4. Leung DYM, Hanifin JM, Charlesworth EN, Li JT, Bernstein IL, Berger WE, et al. Disease management of atopic dermatitis: a practice parameter. Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. Work Group on Atopic Dermatitis. Ann Allergy Asthma Immunol 1997;79(3):197-211.
7. PROTOPIC® (tacrolimus) ointment 0.03%, ointment 0.1%: topical immunomodulator [product monograph]. Markham (ON): Fujisawa Canada; 2001 Jul 18. Control no 067286.
37. European multicentre randomised double-blind comparative study to evaluate the efficacy and safety of 0.03% and 0.11% tacrolimus (FK506) ointment and 0.1% hydrocortisone butyrate ointment in adults with moderate to severe atopic dermatitis. National Research Register 2000;N0217003832.

This brief was prepared by Michel Boucher; CCOHTA and has been peer reviewed. The contents are current as of July 2001.

For updates to the regulatory status of this technology, check the sites in the Links (Regulatory Status) section of our website: www.ccohta.ca

ISSN 1488-6316
Publications Agreement Number 40026386

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is a non-profit organization funded by the federal, provincial and territorial governments.