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Topical Tacrolimus

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New Drug
Spotlight

ABSTRACT

Tacrolimus, available for intravenous, oral and now topical administration, is a potent immunosuppressive agent with the ability to block the production of Interleukin-2 (IL-2) and inhibit T-cell proliferation. Originally developed for use in organ transplantation, it is currently being studied for the treatment of inflammatory dermatoses. The US FDA recently approved tacrolimus ointment (Protopic, Fujisawa) for the treatment of atopic dermatitis.

KEY WORDS: tacrolimus, atopic dermatitis, immunosuppressant

Tacrolimus, previously known as FK506, is an 822-KDa-macrolide antibiotic produced by the fungus *Streptomyces tsukubaensis*. It is a powerful immunosuppressant and although it's not structurally related, tacrolimus exhibits selective antilymphocytic activity similar to cyclosporine, an agent that has revolutionized transplantation medicine and the treatment of selected autoimmune disorders. Currently, tacrolimus is emerging as a promising therapeutic alternative for the treatment of a number of dermatological diseases that have in common an aberrant immunologic response. This topical ointment is the first of its kind to be approved by the US FDA (December 2000), 0.1% for the treatment of moderate-to-severe atopic dermatitis in adults, and 0.03% for children older than 2 years of age and for adults who are undergoing long-term intermittent therapy. Phase III trials are underway in Canada, where a New Drug Submission (NDS) was put forward in July 2000. In Japan, *Protopic* 0.1% was approved in 1999.

Mechanism of Action

Both tacrolimus and cyclosporine interrupt the T-cell receptor mediated signal transduction pathway, which ultimately blocks the production of Interleukin-2 (IL-2) and inhibits T-lymphocyte proliferation. However, *in vitro* studies have shown that when compared to cyclosporine, tacrolimus exhibits 10-100 times greater immunosuppressive activity.¹

During T-cell activation, antigen binds to its specific T-cell receptor causing an increase in intracellular calcium. The calcium ions then bind to the molecule calmodulin resulting in a complex that activates calcineurin. Calcineurin is a calcium dependent

serine/threonine phosphatase that dephosphorylates nuclear factor of activated T-cells (NF-AT). Once dephosphorylated, NF-AT translocates from the cytosol into the nucleus, binds to the promoter region of several cytokine genes (i.e., IL-2, IL-3, IL-4, GM-CSF, TNF-alpha), and induces their transcription.^{1,2}

Tacrolimus acts by diffusing into the cytoplasm and binding to an immunophilin intracellular receptor named FK-binding protein (FKBP). The tacrolimus-FKBP complex then binds to calcineurin and physically blocks the entrance of molecules, such as NF-AT, to its active site. Therefore, in the presence of the tacrolimus-FKBP complex, the phosphorylated NF-AT is unable to translocate into the nucleus. This halts the transcription of IL-2 and other cytokines, thus inhibiting T-cell proliferation.^{1,2}

In addition to its action against T-cell proliferation, *in vitro* tacrolimus demonstrates a direct inhibitory effect on mast cell degranulation. It also seems to inhibit the production of the pro-inflammatory mediator IL-8 and the IL-8 receptor. As well, it decreases the binding of IL-8 to its receptor on keratinocytes. Finally, *in vitro* studies also suggest that tacrolimus enhances the action of the tumor suppressor gene p53.³

Unlike cyclosporine, a molecule which seems to be too large to penetrate human skin, tacrolimus is active topically and appears to target epidermal leukocytes, and antigen presenting epidermal dendritic cells. *In vitro* and *in vivo* studies have shown that topical tacrolimus down-regulates the expression of the high-affinity receptor for immunoglobulin E (IgE) and the costimulatory molecule CD80 in epidermal dendritic cells. It may also interfere with epidermal cytokine networks and TH1/TH2 lymphocyte

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balance. Additional studies are certainly warranted, however, these mechanisms may begin to explain the efficacy of topical tacrolimus for atopic dermatitis.^{1,4}

Pharmacokinetics

When applied to intact human skin, *in vitro* studies have demonstrated that tacrolimus is not readily absorbed. However, on inflamed or damaged skin, it is absorbed in sufficient amounts to be topically active. The agent is metabolized in the liver by Cytochrome P4503A4 and is eliminated almost completely in the bile.^{1,3,5}

Indications & Clinical Trials

Perhaps most exciting is the finding that topical preparations of tacrolimus, in contrast to cyclosporine, are effective for the treatment of certain skin disorders including atopic dermatitis and allergic contact dermatitis. Based on the results of an open trial in 1994, Nakagawa, et al, first reported the safety and efficacy of topical tacrolimus against atopic dermatitis.¹⁴ In this trial, all patients had improved disease severity by day 21. Furthermore, the highest recorded blood level of tacrolimus was 0.9ng/ml, which is significantly lower than the levels (5-20ng/ml) obtained during systemic therapy.⁶ Since that time, multiple controlled and uncontrolled studies have confirmed the safety and efficacy of topical tacrolimus for atopic dermatitis (see Table 1). For example, Alaiti, et al, demonstrated the efficacy of twice daily application of tacrolimus 0.3% ointment over 8 days in 31 adults and 8 children with moderate-to-severe atopic dermatitis. In this study, no systemic accumulation of tacrolimus was observed, 95% of patients showed at least good improvement, and no drug-related changes in laboratory profile were noted.⁷

Additionally, in a randomized, double-blind, multicenter trial that compared 0.03%, 0.1% and 0.3% ointment in 213 patients with moderate-to-severe atopic dermatitis, statistically significant improvement was noted in all treatment groups when compared with the placebo group. However, differences between the three

treatment groups were not statistically significant. In concordance with prior observations, the only notable adverse event during topical tacrolimus therapy was irritation at the treatment site. Furthermore, throughout the investigation most treatment group patients maintained blood concentrations below 0.25ng/ml.⁸

Nevertheless, it should be noted that in one study to examine tacrolimus concentrations in blood during topical treatment of atopic dermatitis, a blood concentration of 20ng/ml was recorded in an erythrodermic patient 6 hours after receiving one application of 10g of ointment with a tacrolimus dosage of 1mg/gm. Although the blood concentrations decreased to 2.9ng/ml by 72 hours and no systemic side effects were observed, this finding may support the utility of laboratory monitoring during topical tacrolimus therapy, especially in patients with an extensively impaired skin barrier.⁹

Because atopic dermatitis is a chronic, relapsing condition in which continuous or repeated use of medications is quite common, an open-label, non-comparative study was recently performed to investigate the safety and efficacy of 0.1% tacrolimus ointment for long-term treatment. Consistent with the results of earlier short-term trials, local irritation (e.g., burning, pruritus, erythema) seemed to be the only adverse event clearly related to the use of tacrolimus ointment, and no systemic side effects were apparent. By 12 months, 86% of patients experienced marked improvement or clearance of disease.¹⁰ Finally, and perhaps most importantly, the safety and efficacy of twice daily application of tacrolimus ointment for pediatric patients was demonstrated in a double-blind, vehicle-controlled multicenter trial of children aged 7-16 years with moderate-to-severe atopic dermatitis.¹¹ This may have important implications for the future approach to atopic dermatitis, the most common chronic skin disease in children.

With regard to allergic contact dermatitis in human volunteers, 0.01-0.1% preparations of tacrolimus suppressed the allergic

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Study	Subjects	Dosage and Regime	n	% improvement	Side Effects
Randomized, double-blind, multicenter ⁸	213 adult patients	• 0.03% bid x 3 wks • 0.1% bid x 3 wks • 0.3% bid x 3 wks • Vehicle bid x 3 wks	• 51 • 54 • 54 • 54	• 75% • 83% • 66.7% • 22.5%	Burning at site; No systemic adverse events noted
Open-label, two-center, phase I ⁷	39 patients aged 5-75 years	0.3% for 8 days, once/day on days 1 & 8 bid on days 2-7	39	95%	Burning at site; Vasodilation (flushing/warmth)
Open-label, non-comparative ¹⁰	316 patients aged ≥ 18 years	0.1% bid • x 6 mos • x 12 mos	• 200 • 116	• 81% • 86%	Burning, pruritus, erythema
Double-blind, vehicle controlled, multicenter ¹¹	180 patients aged 7-16 years	• 0.03% bid x 22 days • 0.1% bid x 22 days • 0.3% bid x 22 days • Vehicle bid x 22 days	• 43 • 49 • 44 • 44	• 72% • 77% • 81% • 26%	No systemic adverse events noted

Table 1: A review of some clinical studies done to determine the efficacy of tacrolimus ointment for the treatment of moderate-to-severe atopic dermatitis.

The Use Of Interleukins For Advanced Melanoma

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ABSTRACT

Treatment of metastatic melanoma using traditional chemotherapy regimens has been disappointing. However, recent work with agents that modify the host's immune system (e.g., interleukins) have provided limited but encouraging results. Interleukins are a group of molecules involved in immune cell signaling. As a high-dose, single agent therapy, Interleukin-2 (IL-2) has produced durable, complete responses in a small, but real percentage of metastatic melanoma patients, but toxicities are significant and specialized care is required. The use of IL-2 in conjunction with other chemotherapeutic and biologic agents has produced an even higher percentage of complete responses, but the trials have been relatively small to date and durability is not as well proven. IL-2 is also being tested in conjunction with vaccines, activated immune cells, and other biologic response modifiers (including IL-12). It is hoped that these will lead to further increases in the number of metastatic melanoma patients who respond in a clinically meaningful fashion.

KEY WORDS: metastatic melanoma, biochemotherapy, Interleukin-2, biologic response modifiers

Historically, metastatic melanoma has had a dismal prognosis, but recent use of biologic response modifiers, e.g., interleukins, to treat this disease has shown promise. The interleukins are a group of molecules involved in the growth, development and maintenance of a number of immune system cells and responses. The most widely studied interleukin in the treatment of metastatic melanoma is Interleukin-2 (IL-2).

IL-2, a 15kD glycoprotein, is produced and secreted by T-lymphocytes to activate and stimulate T-lymphocyte growth.¹ Its effects in melanoma patients appear to be exclusively immune-mediated, as no direct cytotoxic effects on melanoma cells are noted, even at high doses in cell culture.² Current and future therapies involving IL-2 for patients with metastatic melanoma include:

- (a) high-dose single agent IL-2 therapy
- (b) multi-agent combined immunotherapy and chemotherapy (so-called "biochemotherapy")
- (c) IL-2 combined with other immune-modifying agents, including vaccines, activated immune cells, and other biologic response modifiers.

Single Agent IL-2 Therapy

Initial work with high-dose single agent IL-2 therapy in patients with metastatic melanoma was pioneered by Rosenberg.² Additional work by Atkins and others followed,^{3,4} and results from 270 patients with 5-13 years of follow-up are now available.³ IL-2 was administered intravenously at 600,000 or 720,000 IU/kg every 8 hours for up to 14 consecutive doses over 5 days, as tolerated, with a second identical cycle one week later. Additional courses of therapy were then given every 6-12 weeks to stable or responding patients. Toxicities were frequently severe enough to require admission to an intensive care unit, and included hypotension, the so-called "vascular leak syndrome", renal insufficiency, fever, nausea, vomiting, infection, and hepatic

dysfunction.¹ While much has been learned in recent years regarding toxicity and patient selection, high-dose IL-2 therapy still requires management by clinicians experienced in its use. In the above-noted meta-analysis, complete responses were observed in 6% of patients, many of whom have remained durable for years. These results suggest the possibility of a "cure" in a small percentage of patients treated with high-dose IL-2 therapy,⁴ and must be compared to older (e.g., single-agent chemotherapy) regimens, in which 5-year survival is on the order of 1-2%.³

Biochemotherapy

Biochemotherapy involves the sequential or concurrent infusion of multiple chemotherapeutic agents in conjunction with alpha-interferon and IL-2. Some of the most impressive results with this therapy have come from Legha, et al. In a review of 114 metastatic melanoma patients treated with biochemotherapy, 10% of patients achieved complete remissions of at least 4 years duration.⁵ Toxicities can be significant, and include bone marrow suppression, infection, hypotension, constitutional toxicities, and the IL-2-related capillary leak syndrome. These side effects can be managed by experienced clinicians, and admission to an intensive care unit is rarely required. In a typical biochemotherapy regimen, IL-2 doses are moderate (9×10^6 IU/m²/day by continuous IV) compared to the single agent high-dose IL-2 regimens. Some biochemotherapy regimens are even being tested using lower IL-2 doses, making them potentially suitable for an outpatient setting.⁶ However, low-dose single agent IL-2 has not shown clinical effectiveness in melanoma patients,⁴ and so its role in multi-agent therapy must be proven. While extremely promising, all investigations of biochemotherapy to date have involved single institution phase II trials, and follow-up is not as long as it was for the studies of single agent high-dose IL-2 therapy. The results of several prospective, randomized phase III trials^{7,8} of biochemotherapy regimens for patients with metastatic melanoma will mature in the next several years, and are awaited with interest.

Treatment	Dosage Side Effects	% of Complete Responses	
High dose single agent IL-2 therapy	6 x 10 ⁵ – 7.2 x 10 ⁵ IU/kg q8hrs x 14 doses over 5 days. A second identical cycle is repeated 1 week later, and then every 6-12 weeks to stable or responding patients	Toxicity, e.g., hypotension, vascular leak syndrome, renal insufficiency, fever, nausea, vomiting, infection, hepatic dysfunction	6% of patients
Biochemotherapy (at phase III trial stage)	9 x 10 ⁶ IU/m ² /day by continuous IV	Toxicity, e.g., bone marrow suppression, infection, hypotension, constitutional toxicities, IL-2 related capillary leak syndrome	10% of patients
Vaccine (early stage trials)	Immunization using synthetic derivative of gp100 melanoma-associated antigen, then given high dose IL-2	No significant side effects reported	42% objective response
Dendritic cellular immune response vaccine (early stage trials)	Patient's own dendritic cells grown in culture in presence of several melanoma-associated antigens, then injected back into patient in a series of vaccinations	No significant side effects reported	31% objective response

Table 1: Treatment options for metastatic melanoma.

Complete response = all measurable evidence of tumor disappeared for ≥ 1 month.

Partial response = all measurable evidence of tumor reduced by at least 50% for ≥ 1 month.

Objective response = the percentage of all partial and all complete responses in a population.

Future IL-2 Combinations

A number of trials were performed in the late 1980's and early 1990's using high dose IL-2 in conjunction with adoptive transfer of lymphokine-activated killer cells or tumor-infiltrating lymphocytes, but neither was shown to be more efficacious than high-dose IL-2 alone.⁹ However, the work with the tumor-infiltrating lymphocytes led to the discovery of many melanoma-related antigens, now in use in clinical trials involving vaccines. In one recent preliminary trial, 31 patients were immunized using a synthetic derivative of the gp100 melanoma-associated antigen and then given high-dose IL-2.¹⁰ Objective responses of 42% were seen, which is significantly higher than what is usually seen using high-dose single agent IL-2 therapy alone.

Dendritic cells are antigen-presenting cells that produce IL-12 and express IL-2 receptors on their cell surfaces. They promote the cellular immune response and maintain the viability of IL-2 activated T-lymphocytes.⁹ In one recent trial, melanoma patients' dendritic cells were grown in cell culture in the presence of several melanoma-associated antigens, and then injected back into the patients in a series of vaccinations.¹¹ Objective responses were noted in 31% of patients, and future trials in conjunction with IL-2 appear likely.

IL-12, like IL-2, is an interleukin with anti-cancer activity. It is secreted by antigen-presenting cells and activates cytotoxic lymphocytes.⁹ Several small trials of IL-12 in melanoma patients

have been performed recently, including (a) the injection of genetically-engineered fibroblasts that constitutively produce IL-12,⁹ and (b) the reintroduction of melanoma tumor cells into patients that have been transduced with the gene for IL-12 production.¹² In both trials, clinical and immunological responses were noted. Animal studies have confirmed the synergistic antitumor activity of IL-2 and IL-12,¹³ and so human trials involving combinations of these interleukins appear likely.

Summary

Although the prognosis of metastatic melanoma remains grim, treatment with IL-2, either as a high-dose single agent or in conjunction with other chemotherapeutic agents and alpha-interferon as biochemotherapy, appears capable of producing long-term complete remissions in a small percentage of patients. Current research protocols seek to further expand the immune response(s) of melanoma patients to their tumors, and will hopefully lead to an even greater number of patients who achieve meaningful clinical responses in their disease.

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reactions to dinitrochlorobenzene (DNCB) when compared with placebo.¹²

Drug Interactions

Like cyclosporine, tacrolimus is metabolized by the cytochrome P450 system. Therefore, similar to the multitude of potential drug interactions noted with cyclosporine therapy, any substance that affects cytochrome P450 activity may affect the pharmacokinetics of tacrolimus. This list includes, but is not limited to, erythromycin, clarithromycin, clotrimazole, fluconazole, ketoconazole, and danazol, which may increase tacrolimus blood concentrations. On the other hand, rifampin has been shown to decrease tacrolimus blood concentrations. Finally, data has suggested that tacrolimus may interact with nonsteroidal anti-inflammatory drugs resulting in an increased risk of nephrotoxicity.¹³

Adverse Effects

Topically applied tacrolimus is well tolerated and no systemic side effects have been reported. Burning and stinging are the most commonly documented adverse events associated with the ointment, and mild skin irritation that recedes with time has been noted in a minority of patients.^{8,10} Importantly, unlike corticosteroids, tacrolimus does not induce atrophogenic effects, and recent *in vivo* studies demonstrate that it does not affect collagen synthesis.¹

Conclusion

Protopic is the first of a new generation of topical immunomodulators that bring about clinical improvement by modulating the patient's immune response, and is the first to be recommended for approval by the US FDA. It has proven to be safe and effective for the treatment of atopic dermatitis, and unlike cyclosporine, topical preparations of tacrolimus demonstrate efficacy. Of major importance is the possibility that this drug, in contrast to corticosteroids, may not induce skin atrophy. *Protopic* is the first of a new generation of topical immunomodulators that bring about clinical improvement by modulating the patient's

immune response, and is the first to be recommended for approval by the US FDA. It has proven to be safe and effective for the treatment of atopic dermatitis, and unlike cyclosporine, topical preparations of tacrolimus demonstrate efficacy. Of major importance is the possibility that this drug, in contrast to corticosteroids, may not induce skin atrophy.

In Canada, 30gm of an extemporaneously compounded topical formulation of 0.1% tacrolimus is available for \$40CDN. Fujisawa has not yet determined pricing for its new product in the US. They plan to begin marketing *Protopic* in the spring of 2001.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
HIV/AIDS	Lamivudine, Zidovudine and Abacavir <i>Trizivir</i> Glaxo Wellcome	The US FDA approved this anti-HIV drug in November 2000, for the treatment of HIV infection. It is the first drug to combine three anti-HIV medicines into one single tablet and is intended only for patients whose regimen would otherwise include these three drugs.
Antihistamines	Loratidine <i>Claritin</i> Schering-Plough	The US FDA approved this antihistamine in December 2000, for treatment of chronic idiopathic urticaria and seasonal allergies in children ≥ 2 years. This syrup (10mg/10ml) was previously indicated for these symptoms in children ≥ 6 years.
Mouth and Throat Products	Amlexanox 5% paste <i>Aphthera</i> Access Pharmaceuticals	TPP Canada (formerly HPB – Ottawa) granted notice of compliance in December 2000, permitting the sale of this product in Canada. It is indicated for the treatment of aphthous ulcers (canker sores).
Neurotoxin	Botulinum toxin type B <i>Myobloc</i> Elan Corporation	The US FDA approved this injectable solution in December 2000, for the treatment of patients with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with the disorder. Past experience suggests that it will likely attract off-label use for wrinkle correction.
Drug News		
Antihelminthic Techniques	Researchers with the Dept. of General Practice and Primary Health Care at Ghent University in Belgium reported that wet combing (i.e., combing systematically through wet, well-conditioned hair using a fine-tooth comb) is still considered the gold standard for detecting head lice in children. When compared to the traditional scalp inspection technique, wet combing was found to be more effective. Researchers hope that using the wet combing technique will improve the chances of detecting head lice and prevent lice-free children from receiving unnecessary treatment.	
Neurotoxin	At the November 2000 meeting of the American Society of Dermatologic Surgery, Dr. R. Glogau from UCSF reported that 75% of patients in his case study experienced relief from migraine headaches for 4-6 months following injections of <i>BOTOX</i> (botulinum toxin type A, Allergan) to the face, head and neck muscles. This drug has been used for the off-label indications of wrinkles, uncontrolled eye twitching, crossed eyes, muscle spasms and excessive underarm sweating.	
Drug Warning	A possible drug interaction occurred during concurrent administration of nelfinavir (<i>Viracept</i>) and systemic tacrolimus (<i>Prograf</i>) in a 49-year-old male, liver transplant patient. Close monitoring of tacrolimus blood concentrations and adjustment of dosage may be necessary when starting, stopping, or changing the dose of nelfinavir in patients receiving tacrolimus.	

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