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New Drug Spotlight

Imiquimod Applied Topically: A Novel Immune Response Modifier

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ABSTRACT

*Imiquimod (S-26308, R-837) (1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4 amine), an immune response modifier, was approved as a 5% cream (*Aldara, *3M Pharmaceuticals) by the US FDA in February 1997, for the treatment of genital and perianal warts. Drug activity results primarily from induction of interferon alpha (IFN-α) and other cytokines in the skin, which stimulate several other aspects of the innate immune response. Imiquimod also stimulates acquired immunity, in particular the cellular arm, which is important for control of viral infections and tumors. It is expected to be effective where exogenous IFN-α has shown utility, and where enhancement of cell-mediated immunity is needed. Recently presented Phase II clinical studies demonstrated efficacy in treating UV induced skin lesions, basal cell carcinoma, and actinic keratosis. Case studies have reported benefit when treating molluscum and in prevention of keloids after surgery.*

KEY WORDS: *imiquimod, immune response modifier, warts*

The Th1 CMI response is very effective in most people for controlling viral infections and tumors. For example, chicken pox is almost universal and after an outbreak, the varicella zoster virus responsible is carried in the dorsal root ganglia for the rest of the individual's life. Usually, no further lesions occur, except in those 20% of individuals who eventually develop herpes zoster. In another example, epidemiology studies report the Human Papillomavirus (HPV) is a frequently occurring infection with 50-75% of sexually active adults having an antibody response to the virus.[1] About 15% of these individuals carry the virus and a severe outbreak of warts can occur if the cellular immune response is suppressed because of anti-graft rejection drugs following transplantation, anti-cancer chemotherapy, acquiring HIV infection, or in some cases, pregnancy.

Genital warts, the most common viral sexually transmitted disease, was chosen as the first clinical target for imiquimod because injectable interferon alpha (IFN-α) had demonstrated some benefit, and current therapies had not met the physicians' or patients' needs. Patient dissatisfaction was significant due to pain, tissue destruction, high recurrence rates, expense, and the time required for treatment. As well, current treatments only targeted the visible warts and did not treat the underlying HPV infection.

Published results indicate that biopsies from these patients' warts showed little immune recognition, but biopsies from warts undergoing spontaneous regression showed monocytic cellular infiltration and increased Th1 cytokine expression.[2,3] Similar results were seen in patients treated with interferon.[4]

Mechanism of Action

The exact biochemical mechanism of action for imiquimod is not known. However, studies have reported the following evidence:

- In human peripheral blood mononuclear cells (PBMCs), specifically monocytes, imiquimod at a low concentration of 1-5μg/ml induces cytokine production including several subtypes of IFN-α, TNF-α, IL-1, IL-1RA, IL-6, IL-8, IL-10, IL-12 p40, granulocyte colony stimulating factor (G-CSF), granulocyte/macrophage colony stimulating factor (GM-CSF), macrophage inflammatory protein 1-α (MIP-1α), MIP-1ß, and macrophage chemotactic protein (MCP-1).[5,6]
- Topical application of the 1% or 5% cream formulation of imiquimod to the skin of hairless mice increases IFN-α messenger RNA (mRNA) levels, and higher protein concentrations of IFN and TNF-α in the skin at the treatment site.[7,8]

- Topical treatment of hairless mice with imiquimod causes Langerhans cells in the skin to enlarge, appear activated and migrate from the treatment site to the regional lymph node.[9] These activated cells may enhance antigen presentation to T-cells.
- Imiquimod was shown to be effective in animal models against a number of viral infections and a variety of transplantable tumors.[10,11] The duration of antiviral activity lasts for 3-4 days after each oral imiquimod administration and correlates with elevation of oligoadenylate synthetase (2',5'-AS) activity, though this increase is indirect through IFN-α production.[12] Elevated 2',5'-AS was observed in the serum of mice, rats, guinea pigs, monkeys, and humans[7] from 24-72 hours after oral treatment.
- Antitumor activity of imiquimod is also seen in a number of transplantable mouse tumor models[13] Much of this antitumor effect is blocked by administration of antibodies to IFN-α.
- Imiquimod was effective at inhibiting growth of the human mammary tumor MCF-7 when transplanted into nude mice lacking T-cells, indicating that acutely, T-cells are not required for its antitumor effects.[13]
- Although it does not stimulate T-cells to divide, nor does it directly induce T-cell cytokines such as IL-2, IL-4 or IL-5, imiquimod can indirectly stimulate production of the T helper type 1 (Th1) cytokine, IFN-γ, in mouse splenic and bone marrow cultures, as well as human PBMC cultures. Production of IFN-γ in response to imiquimod is inhibited by antibodies to IL-12 and IFN-α, demonstrating the importance of these monocyte/macrophage cytokines.[14] The mechanism of interaction between these cytokines has recently been defined.[15,16] Results show that IFN-α induces the IL-12 receptor β2 subunit on Th1 cells. These cells can then respond to IL-12 and produce IFN-γ. Thus, Th1 cells are the major source of IFN-γ. However, cytotoxic T-cells and natural killer (NK) cells are also able to produce IFN-γ in response to imiquimod.
- Imiquimod was reported to inhibit production of the Th2 cytokine IL-5 in both mouse and human cell systems, and as a result, it has also been found to inhibit both antigen and *Sephadex* induced eosinophilia in several animal models.[17]
- Results from a Phase I double-blind, randomized, parallel group study done in humans showed that all imiquimod treated patients had a ≥75% reduction in wart area.[18] Imiquimod treatment stimulated significant increases in IFN-α as well as increases in TNF-α mRNAs, cytokines previously found to be induced by imiquimod in animal studies[7,10,19,20] and in human PBMC studies.[5,6]

Imiquimod may be useful in atopic diseases as well as other diseases where an increased Th1 response is needed. Wart regression by imiquimod is associated with an induction of local cytokines and cellular infiltrates that are involved with the generation of a cell mediated immune response.

Summary of Clinical Efficacy Trials

A Phase II study of 108 patients with genital warts compared topically applied 5% imiquimod cream to vehicle cream (see Table 1).[21] The imiquimod group had 40% "complete wart clearance" compared to no "complete clearance" in the vehicle group. In addition, there was a median 90% reduction in wart area at the end of treatment among the imiquimod group, but no change in wart area in the vehicle treated group. Patients with totally cleared lesions entered a 10-week follow up period to observe wart recurrence and 81% of the imiquimod treated group remained wart free.

A Phase III multi-centered, randomized, double blind, placebo controlled trial compared the safety and efficacy of imiquimod 5% cream, 1% cream and vehicle.[22] The main outcome measurements were the number of patients experiencing complete elimination of all baseline warts and wart recurrence. The reduction in baseline wart area, the duration of therapy required to eliminate warts, and the frequency and severity of adverse reactions were also monitored. Patients with total wart clearance entered into a 12-week follow up to monitor recurrence. The difference between the effectiveness of the 5% cream and vehicle was statistically significant ($p<0.0001$). The results using 1% cream were not significantly different from vehicle. The median time to clearance was 10 weeks, 12 weeks, and 12 weeks, respectively. Females had a higher clearance rate (77%, 46%, and 28%, respectively) than males (40%, 10%, and 6%, respectively), and females had a shorter median time to clearance (8 weeks) than males (12 weeks) in both imiquimod groups. The better response in females could be due to several factors including shorter duration of warts in females (3.4 months median) vs males (6.7 months median), better compliance for females, or better drug absorption in females. The treatment was well tolerated. Local erythema was the most common adverse reaction (67%, 26%, and 24%, respectively) but the majority of patients experienced no or only mild local inflammatory reactions.

In a second Phase III trial the difference between the effectiveness of the 5% cream and vehicle was also statistically significant ($p<0.0001$), though clearance in the 1% vs the vehicle group was not. Recurrence rates were 19% (9/48) for 5% imiquimod group, 17% (2/12) for the 1% group, and 0% (0/3) for the vehicle group. The low recurrence rate in the vehicle groups is not surprising since the mechanism of spontaneous clearance was shown to be due to immune recognition.[2,3] Local skin reactions were more common and more severe with daily treatment, but there were no systemic adverse reactions. Results were again better in women. Both 3 times/week and daily treatment regimens were acceptable for safety and efficacy, however in the final analysis, most patients preferred the 3 times/week regimen.[23]

Investigator	Trial	n	Application	% Complete Wart Clearance	Recurrence Rate	Adverse Reactions
Beutner, et al (1998 Feb)[21]	Phase II	108 patients with genital warts	23-24 hour application 3 days/wk for 8 wks	5% Imiquimod Cream: 40%	19%	
				Vehicle Cream: 0%	N/A	
Edwards, et al (1998)[22]	Phase III, multicenter, randomized, double-blind, placebo controlled	180 males 131 females ≥ 18 yrs old with 2-50 external anogenital warts	8 hour application overnight, 3x/wk for 16 wks or until totally clear	5% Imiquimod Cream: 50%	13%	Local erythema; no systemic adverse reactions
				1% Imiquimod Cream: 21%	0%	
				Vehicle Cream: 11%	10%	
Beutner, et al (1998 Apr)[23]	Phase III, multicenter, randomized, double-blind, placebo controlled	154 males 125 females with genital warts	8 hour application overnight daily for 16 wks or until totally cleared	5% Imiquimod Cream: 71%	19%	Local erythema; no systemic adverse reactions
				1% Imiquimod Cream: 16%	17%	
				Vehicle Cream: 4%	0%	
Conant, et al (1998)[24]	Multicenter, double-blind, vehicle controlled, parallel group trial	97 males 3 females who are HIV positive and have genital warts	Treated 3x/wk for 16 wks or until totally cleared	5% Imiquimod Cream: 11% (>50% wart reduction: 38%)		Mild erythema
				Vehicle Cream: 6% (>50% wart reduction: 14%)		

Table 1: A review of clinical efficacy trials.

A vehicle controlled safety and efficacy trial was done in HIV-positive genital wart patients.[24] The primary objective of this trial was to evaluate the safety of imiquimod 5% cream in HIV-positive patients. A secondary objective was to assess wart clearance and reduction in the wart area. No local skin reactions were seen in a majority of patients and only mild erythema was seen in most of the others. The difference between the effectiveness of the 5% cream and vehicle was not significantly different. However, there was a statistically significant difference between treatment groups for patients who achieved >50% reduction in wart area, 38% for imiquimod, and 14% for vehicle ($p=0.013$). This was a clinically meaningful reduction in wart area since wart area increases are frequently seen in these patients. These results suggest that in HIV patients, imiquimod induces the innate response that stops wart growth and causes wart area reduction and may, in part, be IFN-α mediated. However, the reduced total wart clearance in HIV patients compared to immunocompetent genital wart patients suggests a role for T-cell responses in initial wart clearance as well as in long term protection from recurrence. Imiquimod has an acceptable safety profile in HIV-positive and AIDS patients.

Imiquimod's mechanism of action should also be effective for treating other chronic virus skin infections such as common warts, plantar warts, herpes simplex virus infection, and molluscum contagiosum, as well as skin tumors. Small studies have reported success in treating molluscum,[25,26] and a case report shows treatment of a patient with recalcitrant facial flat warts.[27] Results of a small pilot trial of imiquimod 5% cream in patients with Bowen's disease showed that 14 of 16 patients cleared their lesions.[28] A pilot study showed success in treating basal cell carcinoma,[29] and Phase II results were recently reported (Geisse, personal communication, 2000 Oct). Phase II results were also reported for actinic keratosis (Stockfleth, personal communication, 2000 Oct). Other skin tumors that might respond include Kaposi's sarcoma and cutaneous T-cell lymphoma since they have been reported to respond to interferon therapy.[30,31]

Since imiquimod inhibits Th2 responses in preclinical animal models, atopic based skin inflammation such as atopic dermatitis might also benefit. Other conditions that have responded to topically applied imiquimod include alopecia areata (Stockfleth, personal communication, 2000 Oct) and keloids (Berman, personal communication, 2000 Oct).

Another possible use for these drugs is application with a vaccine for adjuvant activity. The imidazoquinolines are expected to enhance a Th1 response to the vaccine, which could be beneficial for virus or tumor vaccines. Drug application topically or transdermally could be explored with the injectable vaccine. On the other hand, skin inflammation due to excessive Th1 responses, such as psoriasis and contact dermatitis, might be worsened by topical treatment with imiquimod. Imiquimod is unique in being a topically active cytokine inducer and stimulant for the CMI response.

Conclusion

Wart regression by imiquimod is associated with an induction of local cytokines and cellular infiltrates that are involved with the generation of a cell mediated immune response. These results in humans are consistent with the preclinical results reported in animal models. Overall, imiquimod applied topically is an immune response modifier that would be a useful addition to the drugs that can be used to treat significant chronic conditions of the skin. As such, imiquimod applied topically, represents a new class of drug.

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The Use of Photodynamic Therapy as an Antimicrobial Agent

There is increasing concern worldwide about bacterial resistance to antibiotic therapy. An alternative approach may be the use of antimicrobial photodynamic therapy (APDT), which involves the use of light in the presence of a photosensitizing agent to kill microbes.

B. Zeina, et al, in the *British Journal of Dermatology*[1] reported that they used a combination of methylene blue and visible light against a range of microbial species representative of those encountered on the skin in health and disease. They determined the kill rates for these species (i.e., *Staphylococcus aureus, S. epidermidis, Streptococcus pyogenes, Corynebacterium minutissimum, Propionibacterium acnes,* and *Candida albicans*) and found that it was proportional to the light intensity used.

All the microbial test species were susceptible to APDT, but the eukaryotic species *(C. albicans)* was much less susceptible than were the prokaryotic bacteria. The hypothesized that the reasons for this might be due to the presence of a nuclear membrane, creating an additional barrier, or may also reflect differences in cell size/volume. *Candida* species are about 25-50 times larger than the bacterial test species.

Other investigators studied the effect of PDT using light in the violet-blue range (407-420nm) on *P. acnes* in 35 patients.[2,3] After 8 treatments, 80% of the subjects showed significant improvement in their acne. UV was totally blocked and no side effects were noted.

These initial reports indicate that PDT could be used as a safe and effective procedure enabling the successful treatment of control of a variety of microbe-associated skin diseases.

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National Registry Established for Patients with Alopecia Areata

Alopecia areata is an autoimmune disease that affects more than 4 million people in the US alone, and whose hallmark symptom is unexplained hair loss. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) has established a national registry for patients to provide medical and family history with three major forms of this disease:

- alopecia areata (patchy scalp hair loss)
- alopecia totalis (100% scalp hair loss)
- alopecia universalis (100% scalp and body hair loss).

Families with multiple affected members will be especially helpful in locating the gene or genes associated with this condition.

The registry will serve as a liaison between affected families and investigators who are interested in studying this disorder and serve as a central information source to facilitate research. Patient enrollment is projected to begin in the fall of 2001, and is limited to residents of the US. The registry contact is:

Madeline Duvic, MD.
Phone: 713-792-5999
Fax 713-794-1491
e-mail: alopeciaregistry@mdanderson.org

Update on Drugs

Class	Name/Company	Approval Dates and Comments
Antifungal Agent	**Caspofungin Acetate** *Cancidas* Merck	The US FDA approved this antifungal agent in January 2001, for the treatment of invasive aspergillosis in patients who do not respond to or cannot tolerate other antifungal therapies. It is in a new class of antifungals called echinocandins or glucan synthesis inhibitors, and the first to be approved by the FDA.
Hair Growth	**5% Minoxidil Topical Solution** Alpharma	The US FDA approved this generic version of *Rogaine* (Pharmacia), in November 2000, for the treatment of thinning hair or hair loss in men.
Sunscreens	**Mequinol 2%, Tretinoin 0.1%** *Solagé Topical Solution* Westwood Squibb	TPP – Canada approved this topical agent in January 2001, for the treatment of solar lentigines and related hyperpigmented lesions.
Human Skin Construct	**Biologically Active Dressing** *Composite Cultured Skin (CCS)* Ortec International	The US FDA approved this human skin construct in February 2001, for patients undergoing hand reconstruction to treat recessive dystrophic epidermolysis bullosa, a rare genetic disorder. *CCS* was approved under the Humanitarian Device Exemption Program, which is reserved for devices that treat diseases affecting less than 4000 people in the US.
Depigmenting Agents	*Xtrac Excimer Laser System* PhotoMedex	The US FDA approved an additional indication for this system in February 2001, for the treatment of vitiligo. It was originally approved in January 2001, for the treatment of psoriasis. This system uses UVB radiation and offers an alternative to PUVA, the most popular therapy for vitiligo.

Drug News

Drug Warning	The US FDA is advising manufacturers of vaginal creams and suppositories containing miconazole to add a new warning on product labels advising women who take warfarin (an anticoagulant) to check with their doctor for advice before using these OTC products. The FDA has received reports of women who experienced problems with blood clotting when taking the two drugs simultaneously. Physicians and patients should be aware that patients who need to use both these drugs at the same time should be monitored.
Antiviral Agent	*Abreva* (docosanol 10% cream was launched by SmithKline Beecham (licensed from Avanir Pharmaceuticals) in the US as an OTC treatment for recurrent oral-facial herpes infections.
Anti-acne Agent	Dermik Laboratories launched its new combination acne therapy, *BenzaClin Topical Gel* (clindamycin 1% and benzoyl peroxide 5%) in February 2001. In clinical studies this drug was shown to be significantly more effective that either clindamycin or benzoyl peroxide alone in treating acne. *BenzaClin* is now available by prescription in the US.
Neurotoxin	Athena Neurosciences, a division of Elan Pharma launched *NeuroBloc* (botulinum toxin type B) in the UK in February 2001. It is the first treatment for cervical dystonia that contains the type B form of this neurotoxin.

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