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Safety, Efficacy & Recurrence Rates of Imiquimod Cream 5% for Treatment of Anogenital Warts

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ABSTRACT

Imiquimod 5% cream (Aldara™, Graceway Pharmaceuticals) is an immune response modifier used for the topical treatment of anogenital warts in non-HIV-infected patients. Several randomized controlled trials have demonstrated that imiquimod 5% cream is a safe and efficacious treatment. Current data regarding efficacy shows that complete clearance of warts occurred in up to 50% of patients treated with imiquimod 5% cream applied once-daily, 3 times per week for up to 16 weeks. Recurrence rates ranged from up to 19% at 3 months to 23% at 6 months. Imiquimod 5% cream showed an acceptable safety profile; local inflammatory reactions were the most frequent adverse effects, with local erythema being the most common.

Keywords: anogenital warts, HPV, human papillomavirus, imiquimod

Imiquimod is an immune response modifier that was approved by the US FDA in 1997 for the topical treatment of anogenital warts in individuals 12 years old and older. An estimated 30%-50% of sexually active adults in the US are infected with human papillomavirus (HPV), and approximately 1%-2% of this same population have clinically evident genital warts.[1] This review will focus on studies that evaluate the safety, efficacy, and recurrence rates of imiquimod 5% cream in the treatment of anogenital warts in non-HIV-infected men and women. Local inflammatory reactions were the most frequent adverse effects, with local erythema being the most common. Overall, imiquimod 5% cream is a safe and efficacious treatment for anogenital warts.

Using Imiquimod

Imiquimod cream is supplied in individual packets. Each gram of the 5% cream contains 50mg of imiquimod in an off-white oil-in-water vanishing cream base.[2] The US Center for Disease Control recommends that imiquimod 5% cream be applied once daily at bedtime, 3 times per week for up to 16 weeks. The product should be washed off with mild soap and water 6-10 hours following application.[2-4] Many considerations exist when using imiquimod. Some of these are listed in Box 1. The US FDA provides a full list of considerations.[3]

Mechanism of Action

Imiquimod is a Toll-like receptor agonist that induces the production of local cytokines from predominantly T helper (Th) 1-type cells, thus stimulating both acquired and cellular immunity, which is important for fighting virus-infected and tumor cells.[5-7] Cytokines such as interferon (INF)-α, tumor necrosis factor (TNF)-α, interleukin (IL)-1, -6, -8, -10, and -12 stimulate tissue-specific apoptosis of virus-infected keratinocytes, thus leading to a viral load reduction of HPV types 6 and 11 with subsequent wart regression and normalization of keratinocyte proliferation.[5,6,8] Regression of warts after treatment with imiquimod is strongly associated with evidence of tissue production of INF-α, -β, and -γ and TNF-α as well as a decrease in the presence of HPV DNA and in the expression of mRNA for both early and late viral proteins.[9]

Points to consider when using imiquimod:

- It is common for patients to experience local skin reactions and treatment can be resumed after the skin reaction has subsided.
- Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin.
- Imiquimod may weaken condoms and vaginal diaphragms, therefore concurrent use is not recommended.
- Imiquimod is pregnancy category C and it is not known whether topically applied imiquimod is excreted in breast milk.
- New warts may develop during therapy, as imiquimod is not considered a cure.

Box 1: Information for patients being treated for external genital warts[3]

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Safety

In all the randomized controlled trials (RCTs) examined, topical imiquimod 5% cream showed an acceptable safety profile. Local skin reactions are associated with a local inflammatory reaction including itching, erythema, burning, irritation, tenderness, ulceration, erosion, and pain.[10] In several studies, local erythema was the most common reaction.[11-13] There were no differences in adverse systemic reactions or flu-like symptoms among treatment groups.[10,12,13] The optimal dosing regimen is 3 times per week. With more frequent applications (up to 3 times daily), wart clearance does not improve significantly and is associated with an increase in local adverse events, such as erythema, vesicle formation, ulceration, and excoriation.[14] Imiquimod 5% cream is effective for up to 16 weeks of treatment for external anogenital warts and is well-tolerated for up to 32 weeks.[11] Imiquimod is contraindicated in individuals with a history of sensitivity reactions to any of its components and should be discontinued if hypersensitivity to any of its ingredients is noted. Overall, patient-applied imiquimod 5% cream is an effective treatment for external genital warts and has a favorable safety profile.

Efficacy and Recurrence

Several randomized controlled trials demonstrated that imiquimod 5% cream is an efficacious treatment for external anogenital warts when applied 3 times per week for up to 16 weeks. Complete clearance of warts occurred in up to 50% of patients treated with imiquimod 5% cream applied 3 times daily. At the end of 16 weeks, recurrence rates ranged from up to 19% after 3 months and 23% after 6 months.[11] See Table 1 for comparisons. The recurrence rates of external genital warts were found to be similar at both 3- and 6-month follow-up, suggesting that after 3 months, the risk of developing recurrence is low.[15]

The studies that follow were chosen to evaluate imiquimod 5% cream for the treatment of anogenital warts because of sufficient data on efficacy, recurrence rates, and safety.[10-13] Studies that did not include this data were excluded. Several other studies focused on the treatment of anogenital or vulvar warts in the female population; however, the efficacy rates are generally higher for this population, ranging from 71%-77%.[12,16-18] To maintain continuity, this review focuses on comparing studies that include treatment of anogenital warts with imiquimod 5% cream in non-HIV-infected men and women.

Beutner, Spruance et al.[10]

In a prospective, double-blind, placebo-controlled, clinical trial with 108 patients, imiquimod 5% cream was applied 3 times daily for up to 8 weeks. Complete wart clearance was achieved in 37% of the imiquimod-treated patients and 0% of the placebo group. Many patients experienced a partial response: an 80% or more reduction in baseline wart area was achieved in 62% of imiquimod-treated patients versus a 4% reduction in the placebo group. A 50% reduction in baseline wart area was noted in 76% of imiquimod-treated patients compared with 8% of the placebo group. For patients whose warts cleared completely, 19% experienced recurrences after a 10-week follow-up period. There were no differences in systemic reactions between treatment groups. Local inflammatory reactions were predominantly mild or moderate in severity and included itching (54%), erythema (33%), burning (31%), irritation (17%), tenderness (13%), ulceration (10%), erosion (10%), and pain (8%).

Garland et al.[11]

In an open-label phase IIIB trial consisting of 943 patients in 20 countries, imiquimod 5% cream applied 3 times per week was found to be 47.8% effective for overall complete clearance after 16 weeks of treatment. Recurrence rates at the end of 3- and 6-month follow-up were 8.8% and 23%, respectively. The sustained clearance rates (patients who cleared during treatment and remained clear at the end of the follow-up period) after 3 and 6 months were 41.6% and 33%, respectively. The study also found that a greater proportion of female patients (75.5%) experienced complete clearance than did male patients (56.9%). At least 1 adverse event was reported in 42% of patients; the majority of reactions were mild to moderate in severity. Local erythema was the most common local skin reaction, occurring in 67% of patients.

Study	# Patients Receiving Imiquimod 5% Cream	Dosing Interval	Complete Clearance Rate	Length of Treatment	Recurrence Rates After Treatment
Beutner, Spruance et al.[10]	108	3 times/week	37%	8 weeks	19% at 10 weeks
Garland et al.[11]	943	3 times/week	47.8%	16 weeks	8.8% at 3 months 23% at 6 months
Edwards et al.[12]	109 / 311	3 times/week	50%	16 weeks	13% at 3 months
Beutner, Tyring et al.[13]	94 / 279	Once daily	52%	16 weeks	19% at 3 months

Table 1: Comparison of studies involving imiquimod 5% cream for treatment of anogenital warts

Edwards et al.[12]
Another RCT consisting of 311 patients was randomized to 3 arms: imiquimod 5% cream, imiquimod 1% cream, or vehicle 3 times per week for a maximum of 16 weeks. Complete clearance of lesions was achieved in 50% of patients who received the imiquimod 5% cream, 21% of those who received imiquimod 1% cream, and 11% of those treated with the placebo. After a 3-month follow-up, the study found a recurrence rate of at least 1 wart in 13% of patients who receive imiquimod 5% cream. The majority of patients experienced no or mild local inflammatory reactions, with local erythema being the most common. Local adverse reactions, which were moderate or severe in intensity after being treated with imiquimod 5% cream, included erythema (40%), erosion (10%), excoriation (7%), edema (2%), and scabbing (5%).

Beutner, Tyring et al.[13]
In another prospective, multicenter, double-blind, RCT with 279 patients, 94 patients used imiquimod 5% cream once-daily for up to 16 weeks. Complete wart clearance was achieved in 52% of patients treated with imiquimod 5% cream, but 19% of these patients had a recurrence at a 3-month follow-up. These results are similar to those obtained with 3 applications per week. When patients were treated with 5% imiquimod cream vs. vehicle, local adverse reactions included erythema (66% vs. 9%), excoriation (21% vs. 4%), erosion (32% vs. 1%), edema (18% vs. 1%), scabbing (18%), induration (5%), ulceration (10%), and vesicles (3%).

Support for Comparable Efficacy in Clearance Rates After 3 Weeks

Garland et al.[11] found that a 1-month treatment course of imiquimod 5% cream applied 3 times weekly for women with external genital warts has comparable efficacy to a 4-month treatment with no statistically significant difference in complete clearance rates (i.e., 40% after 1 month and 51.6% after 4 months). The 1-month treatment had a lower incidence of local skin reactions, such as erythema, and no pain.[18]

Monotherapy Compared with Combination Therapy: Imiquimod + Surgery

Carrasco et al.[19] showed that treatment with imiquimod 5% cream followed by excision of remaining warts resulted in a lower recurrence rate compared with surgery alone. This strategy represents a viable option for those with residual lesions and may provide long-term clearance of anogenital warts in patients for whom imiquimod monotherapy is insufficient.[19]

Conclusion

Patient-applied imiquimod 5% cream is a first-line topical treatment for anogenital warts that is both safe and efficacious, and yields complete and partial responses in the majority of patients. Various studies demonstrate complete clearance rates of up to 50% and partial responses manifest as a 50%-90% reduction in baseline wart area.[12-14] Recurrence rates range up to 19% at 3 months and 23% at 6 months. More studies are needed to compare the efficacy of combination therapies vs. monotherapy vs. other treatment modalities. Longer follow-up is also needed to evaluate recurrence rates after monotherapy, as well as in combination with other treatments for anogenital warts.

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Prevention of Infrared-A Radiation Mediated Detrimental Effects in Human Skin

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ABSTRACT

Photoaging and skin damage that is caused by solar radiation is well known. We have recently learned that within the solar spectrum this damage not only results from ultraviolet (UV) radiation, but also from longer wavelengths, in particular near infrared radiation. Accordingly, infrared radiation (IR) has been shown to alter the collagen equilibrium of the dermal extracellular matrix in at least 2 ways: (1) by leading to an increased expression of the collagen degrading enzyme matrixmetalloproteinase-1 while (2) decreasing the de novo synthesis of the collagen itself. Infrared-A (IRA) radiation exposure, therefore, induces similar biological effects to UV, but the underlying mechanisms are substantially different. IRA acts via the mitochondria and therefore protection from IR requires alternative strategies.

Keywords: infrared, photoaging, skin aging, solar radiation

Physics of Infrared (IR) Radiation

Solar radiation in wavelengths of 290nm to 4000nm reaches the earth's surface after atmospheric filtering. This part of the electromagnetic spectrum is divided into 3 major bands:

- ultraviolet (UV) radiation (290-400nm)
- visible light (400-760nm)
- IR radiation (760-4000nm)

IR is further divided into IRA (760-1440nm), IRB (1440-3000nm), and IRC (3000nm-1mm). Of the total amount of solar energy reaching the human skin, 54% is IR, while only 7% is UV.[1] Roughly 30% of the total solar energy is IRA, which penetrates deeply into the human skin.[1] Most of the IRA radiation load on human skin is of solar origin, but in recent years artificial IRA sources are used increasingly. In addition to therapeutic approaches, the use of IRA for wellness and lifestyle purposes is steadily rising.

Detrimental Effects of IRA and Underlying Molecular Mechanisms

More than 20 years ago, Kligman reported that IR in guinea pigs causes actinic skin damage that resembled skin damage caused by UV.[2] This observation has since been confirmed in another animal model.[3] Moreover, IRA was reported to interfere with apoptotic pathways, thus preventing UV-damaged cells from executing programmed cell death, which indicates a co-carcinogenic potential for IRA.[4,5] Until now *in vivo* carcinogenesis studies for IRA alone and in combination with other noxae like UV have not been published. For IRC, the occurrence of a skin lesion described as erythema ab igne, which may progress to squamous cell carcinoma, has been reported.[6] However, interference with apoptotic pathways,[4] involvement in the repair of damaged DNA,[5] stimulation of proliferation and accelerated woundhealing[7] underline the necessity to further investigate the role of IRA in photocarcinogenesis.

The molecular basis of IRA induced photoaging of the skin was assessed by Schieke et al,[8] who were the first to show that physiological doses of IRA lead to a disturbance of the dermal extracellular matrix by upregulation of the expression of the collagen degrading enzyme matrixmetalloproteinase-1 (MMP1). This finding was confirmed in independent *in vivo* and *in vitro* studies by different laboratories.[9,10] In addition, IRA exposure was recently shown to lead to a downregulation of collagen *de novo* synthesis.[11] The IRA-induced upregulation of MMP1 was found to be different from that induced by UV at the mechanistic level, since it involves the formation of mitochondrial reactive oxygen species (ROS) and the subsequent initiation of a retrograde signaling response (i.e., from the mitochondria to the nucleus) in human skin.[12,13] The omnipresence of IRA, its biophysical properties, and the fact that it acts differently from UV points to the necessity of including specific IRA-directed strategies in modern sunscreens.

Protection Strategies Against IRA

Complete photoprotection of human skin must include protection against IRA. Currently there are no specific chemical or physical filters directed against IRA that are available, or at least the available compounds need to be tested for their IRA-filtering capacity. While it is unlikely, that UV-specific filters work against IRA, physical filters might provide protection in addition to their potential against UV. Controlled studies determining the effectiveness of UV filters in IRA protection are currently not available.

An alternative approach for photoprotection against IRA is the use of antioxidants, especially mitochondrially-targeted antioxidants, e.g., epigallocatechin gallate (found in grape seed extracts and tea extracts), and mitoquinone (MitoQ™, Antipodean Pharmaceuticals), which is a coenzyme Q derivative. Accordingly, topically applying such antioxidants on human skin *in vivo* prior to IRA treatment has shown that it significantly abrogates the IRA-induced detrimental shift in dermal gene expression.[10]

Conclusion

Recent data clearly indicate that in addition to UV, protection against IRA must be taken into account when it comes to modern sun protection. IRA photoprotection requires specific strategies because existing UV protective measures miss the problem. A feasible and effective approach is the topical application of mitochondrially-targeted antioxidants. In addition, unnecessary exposure to IRA radiation from artificial irradiation devices should be avoided.

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Update on Drugs

Name/Company	Approval Dates/Comments
Golimumab *Simponi*™ Centocor/Schering-Plough	The US FDA and Health Canada approved this biologic in April 2009 for the treatment of moderate-to-severe rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.
Darunavir *PREZISTA*™ Tibotec/Janssen-Ortho	Health Canada approved this antiretroviral agent in April 2009 for the treatment of HIV infection to be used once-daily in treatment-naïve adults in combination with other antiretroviral agents such as ritonavir. This product, dosed at 600mg twice-daily, coadministered with 100mg ritonavir twice-daily, is already approved for treatment-experienced patients.
Telavancin *Arbelic*™ Theravance/Astellas	The US FDA accepted in April 2009, as complete for review, Theravance's response to the February 2009 Complete Response Letter, which outlined requirements for approval of telavancin for the treatment of complicated skin and skin structure infections. The FDA's approval will allow Theravance to advance their application through the FDA review process.

Drug News

In February 2009, The US FDA notified the manufacturers of licensed botulinum toxin (BTX) products that there is a need to strengthen warnings in product labeling and add a boxed warning that details the risk of adverse events when the effects of the toxin spread beyond the injection site. In addition, the FDA has advised the manufacturers that development and implementation of a Risk Evaluation and Mitigation Strategy is necessary to ensure that the benefits of the product outweigh the risks. This strategy would include a communication plan to provide more information about the risk for distant spread of the BTX effects after local injection, as well as information to explain that BTX products cannot be interchanged. This strategy would also include a medication guide that explains the risks to patients, their families and caregivers. The FDA is requiring the manufacturers to submit safety data after multiple administrations of the product in a specified number of children and adults with spasticity to assess the signal of serious risk regarding distant spread of toxin effects. BTX products are FDA-approved for temporary improvement in the appearance of glabellar lines, treatment of strabismus, blepharospasm, cervical dystonia, and primary axillary hyperhidrosis. The FDA urges both healthcare professionals and patients to report side-effects from these products to the FDA's MedWatch Adverse Event Reporting Program, online at www.fda.gov/medwatch/report.htm.

Trubion Pharmaceuticals, in collaboration with Wyeth Pharamaceuticals, announced in March 2009 that it has initiated a Phase I/II dose-escalation clinical trial for SBI-087, a humanized small modular immunopharmaceutical drug candidate that acts against the CD20 antigen, for the treatment of systemic lupus erythematosus (SLE). The study will enroll patients who were diagnosed with SLE more than 6 months before the beginning of the study. Diagnosis is based on the American College of Rheumatology Revised Criteria. In preclinical data, a single dose of SBI-087 resulted in dose-dependent B-lymphocyte depletion in peripheral blood and lymphoid tissues that was more profound and sustained when compared with rituximab.