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PRE-ASSESSMENT Imiquimod Cream: Place in Therapy

Before CCOHTA decides to undertake a health technology assessment, a pre-assessment of the literature is performed. Pre-assessments are based on a limited literature search; they are not extensive, systematic reviews of the literature. They are provided here as a quick guide to important, current assessment information on this topic. Readers are cautioned that the pre-assessments have not been externally peer reviewed.

Introduction

Imiquimod 5% cream is indicated in Canada for the treatment of external genital and perianal warts and condylomata acuminata in adults.[1] Many off-label uses have been reported in published trials and case reports. Given the high cost of this medication (a box containing 12 sachets of 250 mg each costs $137)[2] and the fact that most of the conditions for which it is being tried have alternative treatments, the market for this medication may be growing inappropriately. This may be of concern for provincial drug plans with open listings of Aldara™.

In the United States, the manufacturer of Aldara™ (3M) has submitted a supplemental new drug application for the treatment of actinic keratosis (AK) and superficial basal cell carcinoma (sBCC).[3,4] In Canada, a request was made in July 2003 to Health Canada for expansion of the current indication to include AK. It is expected that 3M will also be making an application to include sBCC.[5]

Research Questions

- To establish all the potential off-label uses as reported in the published literature
- To review the evidence pertaining to the efficacy and side effects of imiquimod 5% cream used in dermatological conditions
- To determine the feasibility of undertaking a health technology assessment (HTA) report on the use of imiquimod 5% cream for the indications that have been studied in randomized controlled trials (RCTs).

Assessment Process

Published literature was identified by searching MEDLINE® via PubMed (1966 to 11 August 2003). Retrieval was not limited by language. The CD-ROM version of The Cochrane Library (2003 Issue 3) was also searched.

Grey literature was obtained by searching the web sites of regulatory agencies, HTA agencies, near-technology assessment agencies and clinical trials registries. Google™ and other Internet search engines were used to search for web-based information.

The summary of findings was partly based on an evaluation prepared by Denis Bélanger of the Ottawa Valley Regional Drug Information Service.

Summary of Findings

Researchers have studied the use of imiquimod cream for a variety of dermatological conditions including AK, BCC, squamous cell carcinoma (SCC), molluscum contagiosum and non-genital warts (see Appendix 1). The studies ranged from case reports to randomized, double-blind, vehicle-controlled trials. Treatment regimens ranged from twice daily to once weekly applications. Although its use seems to be promising for a few conditions such as non-melanoma skin tumours, only a handful of diseases were studied in RCTs. Comparators were limited to placebo but not to standard treatment. Long-term outcomes, such as the potential for recurrences beyond 24 weeks, are unknown.

Actinic Keratosis: There have been two unpublished randomized, double-blind, vehicle-controlled studies (n=436); one published randomized, double-blind, vehicle-controlled study (n=36) in which patients were followed for a year; and two open-label studies. Results showed statistically significant reduction or complete clearance of lesions. Notice of Compliance has been requested from Health Canada.

Basal Cell Carcinoma: There have been two unpublished randomized vehicle-controlled studies (n=724); one published randomized, double-blind, vehicle-controlled study (n=128); three phase II dose-funding studies; one Cochrane Review on the treatment of sBCC in general; and many case reports and series. Imiquimod seems to be more effective in sBCC compared with nodular BCC, but there are no long-term outcomes, as studies lasted 16 weeks or less. 3M will be submitting a supplemental new drug application to Health Canada.

Herpes Simplex: In one RCT, imiquimod does not seem to be effective in preventing recurrent herpes genitalis.

Molluscum Contagiosum: No RCT has been done. Preliminary results from open-label studies seem to be promising.

Non-genital Warts: In three open-label studies and many case reports, imiquimod seems to reduce the size of warts and may eradicate the lesion. The success of treatment appears to be related to the site of infection.

Squamous Cell Carcinoma and Bowen's Disease: Only one phase-II, open-label trial of 16 patients exists, but there are many case reports and series. Although preliminary results are promising, it is too early to draw a conclusion on the use of imiquimod in SCC or Bowen's disease.

Vulvar Intraepithelial Neoplasia: No RCT was found. Preliminary reports show that the side effects seem to affect the duration of treatment and hence efficacy.

Other Off-label Uses: Many other off-label uses are reported with varying success.

Conclusion

RCTs were conducted in patients with AK and sBCC. There was evidence of efficacy when compared to placebo. There was no RCT comparing imiquimod cream to standard treatment.

Given that these indications are being considered for Notice of Compliance, it is suggested that CCOHTA produce an "Issues in Emerging Health Technologies" bulletin on the use of imiquimod 5% cream for both conditions. Themes to be considered in the bulletins should include safety, quality of the studies, long-term outcomes, potential for recurrence and place in therapy.

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APPENDIX 1

Actinic Keratosis: AK is a skin tumour induced by exposure to sunlight. It may eventually lead to skin cancer.

In an American news release available on 3M's web site, it is stipulated that the submission for an expanded indication is based on the results from two randomized, double-blind, placebo-controlled trials involving 436 patients with AK. Aldara™ or placebo was applied twice weekly for 16 weeks. On assessment eight weeks after the cessation of treatment, 50% of the patients in the active treatment arm had 83% or greater reduction of the number of lesions when compared with baseline. Complete clearance of the lesions was evident in 45% and 3% of the Aldara™ and placebo groups respectively.[3]

Stockfleth *et al.* conducted a randomized, double-blind, vehicle-controlled study of imiquimod cream in the treatment of multiple AKs. Patients applied the 5% cream three times a week for 12 weeks. The results were analyzed on a per-protocol basis (n=36). The authors reported that of those who were in the active treatment arm, 84% (21/25) were judged by histopathologic examination to have complete clinical clearance. The size and number of lesions in the vehicle arm did not change during the study. After a year, two patients experienced recurrences. No systemic effects were reported, but all patients receiving imiquimod experienced skin reactions, while 52% needed a rest period or a diminution in the frequency of application during the study.[6]

Salasche *et al.* conducted an open-label trial where patients with facial or scalp AK received imiquimod 5% once daily, three times a week, over four weeks, which was followed by a rest period of four weeks. The design involved treatment until there was complete clearance of AK in the treated region or until there had been three cycles. Overall, 25 patients were enrolled and 33 regions of treatment were involved. On intent-to-treat analysis, 82% of sites were judged to be completely cleared; all were achieved within the first or second cycle.[7]

Persaud *et al.* published a small-scale vehicle-controlled trial on the use of imiquimod cream in the treatment of AK. Twenty-two patients with lesions on the face, arms or legs applied vehicle on half of the area affected and imiquimod to the other half. Areas were treated thrice weekly for eight weeks, but this could be minimized to twice weekly if deemed necessary based on adverse effects. Seventeen patients completed therapy (i.e., treatment and eight weeks of post-treatment observation). The average number of lesions per patient diminished from 10.1 to 6.2 and 8.1 to 7.6 with active and placebo intervention respectively ($p<0.005$).[8]

Basal Cell Carcinoma: The efficacy of imiquimod in the treatment of nodular BCC and superficial BCC (sBCC) has been reported in open-label trials, placebo-controlled trials and preliminary case series. Imiquimod cream is included in a Cochrane Review on interventions used for BCC.[9]

At the 61st annual meeting of the American Academy of Dermatology, phase III data involving two trials and 724 patients by Naylor et al. were presented. Patients with sBCC were randomized to receive imiquimod 5% topically five times per week or matching placebo in one study and daily in the other study, for 12 weeks. Histologically confirmed clearing was noted in 82%, 79% and 3% for the five times weekly, daily or placebo groups respectively.[10]

Geisse *et al.* assessed the efficacy of imiquimod 5% in a double-blind, randomized, vehicle-controlled trial. Patients with sBCC received imiquimod (n=96) in one of four dosing regimens (twice daily, once daily, five times per week or three times per week) or placebo (n=32) for 12 weeks. Complete response rates were seen in all patients treated twice daily (10/10), in 87.1% of patients treated once daily (27/31), in 80.8% of patients treated five times weekly (21/26) and in 51.7% of patients treated three times weekly (15/29). The placebo group had a complete response rate of 18.8% (6/32).[11]

The results of two studies examining the efficacy of imiquimod for sBCC and nodular BCC were reported by Sterry *et al.* Patients (n=183) received topical treatment with imiquimod 5% either two days or three days per week, with or without occlusion, for six weeks. After a 12-week follow-up, the response rates in the sBCC group were 87%, 76%, 43% and 50% with three days per week, two days per week, with occlusion or without occlusion respectively (p=0.004 between three times and two times weekly with occlusion only). Those with nodular BCC showed a 65%, 50%, 50% and 57% complete response rate with three times and two times weekly dosing with or without occlusion respectively [p=ns (not significant) between the groups].[12]

Shumak *et al.* described their experience in two phase II studies, one of six weeks duration (n=99) and one of 12 weeks (n=92). The studies were designed to determine the optimal dose of imiquimod cream in the treatment of primary nodular BCC. The authors concluded that applying imiquimod once daily gave the highest histologic clearance rate.[13]

Marks *et al.* published a phase II dose-response trial of 99 patients with sBCC randomized to different treatment regimens (twice daily; daily; twice daily, three times per week; and once daily, three times per week), for six weeks. Histologic clearance was achieved in 100% (3/3) of patients in the twice daily group, in 87.9% (29/33) of patients using daily application, in 73.3% (22/30) of patients in the twice daily three times per week group and in 69.7% (23/33) of patients in the once daily three times per week group.[14]

Beutner *et al.* conducted a pilot trial of 35 patients randomized to five treatment regimens (twice daily, once daily, three times weekly, twice weekly or once weekly) or vehicle cream for a period not extending beyond 16 weeks. Histologic evaluation showed that 20 of the 24 patients receiving treatment were completely cleared of tumours.[15]

Case reports and series were also described for nodular BCC and sBCC.[16-23]

Herpes Simplex: One phase II randomized, double-blind, placebo-controlled study looked at the use of imiquimod cream in recurrent herpes genitalis (n=124). The primary endpoint measured was time to recurrence after treatment. The findings were not statistically significant.[24]

Molluscum Contagiosum: Molluscum contagiosum is an infection of the skin caused by a poxvirus. It manifests as skin-coloured papules and mostly affects children. When seen in adults, it is considered to be a sexually transmitted disease.

Several published open-label studies and case reports examine the value of imiquimod in molluscum contagiosum.

An open-label study was conducted by Barba *et al.* to assess the safety of imiquimod for molluscum contagiosum in children. Thirteen patients applied imiquimod cream daily in the evening, with subsequent removal in the morning, for four weeks. Twelve patients completed the study, with one withdrawing due to intolerable adverse effects. Of the remaining 12, five did not seem to experience any adverse effects. Erythema at the lesion site was the most common complaint among the others. Systemic toxicity was not noted. Complete resolution of the treated lesion was reported in four patients (33%).[25]

Another open-label study was conducted by Liota *et al.* in 39 patients to assess the efficacy of imiquimod. The cream was applied three times per week at bedtime and washed off in the morning, for a maximum of 16 weeks. Thirty-one of the 39 patients showed resolution of their disease.[26]

Hengge *et al.* looked at the safety and efficacy of imiquimod 5% in the treatment of common warts (n=50) and molluscum contagiosum (n=15). Patients were instructed to self-apply imiquimod once daily, for five consecutive days, to a maximum of 16 weeks. In the 15 patients with molluscum contagiosum, 53% of those treated noted a complete clearance of lesions, with another 27% having a greater than 50% reduction in lesion size. Of the successfully treated patients, one developed new molluscum contagiosum in a treated region. Generally, adverse effects were short-lived, mild, local inflammatory reactions.[27]

One double-blind, vehicle-controlled study examining the use of a 1% imiquimod analogue cream in 100 patients has been published. Patients applied the cream or placebo three times daily, five times per week, for four weeks and were followed for nine months. The study showed favourable results with 49/50 of treated patients cured ($p<0.001$) and one relapse at nine months.[28]

Case reports were also described for this condition, including three reports on patients with HIV.[29-34]

Non-genital Warts: Non-genital warts, which are also called verrucae, are caused by human papillomavirus (HPV).

In the Hengge *et al.* study of imiquimod 5% in the treatment of common warts (n=50) and molluscum contagiosum (n=15), 30% of the patients with common warts were judged to have total clearance. Twenty-six percent of patients had a greater than 50% reduction in the size of the wart(s). Those with warts on the feet had the lowest percentage of success. Recurrence was not noted in these patients, but 6% developed new lesions located in non-treated areas.[27]

Grussendorf-Conen *et al.* completed an open-label study in 38 patients with resistant cutaneous warts (mean duration of condition=6.7 years). After using imiquimod 5% twice daily for a period not exceeding 24 weeks, 10 patients out of 37 had a complete clearing of their warts, while 18 patients had a reduction of at least 50%.[35]

The same group reported on the use of twice daily imiquimod 5% for recalcitrant common warts (duration two to seven years) in children. Sixteen of the 18 patients had total clearance of their warts after a mean duration of treatment of 5.8 months.[36]

There were many case reports on the use of imiquimod cream alone or in combination with other treatments, for common warts of the feet, the fingernails, the face and the hands in children and adults.[37-44]

Squamous Cell Carcinoma and Bowen's Disease: Bowen's disease is a squamous cell carcinoma (SCC) that is localized to the site of origin.

Mackenzie-Wood *et al.* reported the results of a phase II, open-label study assessing the efficacy of imiquimod in the treatment of biopsy-confirmed Bowen's disease. Patients (n=16) applied imiquimod 5% cream once daily, for 16 weeks. Overall, 15 patients completed the treatment and had excisional biopsy six weeks later. On intent-to-treat analysis, 87.5% of patients (14/16) had no residual tumour documented. Skin reactions were documented in 94% of patients, leading to an early cessation of treatment for six patients.[45]

There were several case reports and series described: one report with renal transplant patients who used 5% 5-Fluorouracil (5-FU) cream with imiquimod cream;[46] four reports with patients suffering from SCC of the penis;[47-50] one report of a woman with SCC of the thumb;[51] one report of five patients treated with a combination of sulindac and imiquimod cream;[52] and one report of an HIV-positive man treated with a combination of 5% 5-FU cream and imiquimod cream.[53]

Vulvar Intraepithelial Neoplasia: Vulvar intraepithelial neoplasia (VIN) is a precursor for SCC and is related to infection with HPV.

Todd *et al.* conducted a prospective observational study in which 15 patients with biopsy-confirmed high-grade VIN applied 5% imiquimod cream to the affected area(s) three times per week, for a period not exceeding 16 weeks. At six months post-recruitment, a punch biopsy was performed. Of the 13 patients who completed the study, four showed visible improvement in their condition and three of these patients had eradication evident on biopsy. At nine months, however, all four responders had relapsed. The poor efficacy may be explained by the fact that patients had to decrease the frequency of application to twice and once weekly because of local side effects.[54]

van Seters *et al.* observed some success with imiquimod in the treatment of 15 women with multifocal high-grade VIN, where a complete response was observed in four patients and a partial response in nine women. Treatment regimens varied from one to three times per week, with a rest period of one to eight weeks, depending on the side effects. The maximum duration was 30 weeks.[55]

Jayne *et al.* reviewed 13 charts of women with VIN who were treated with imiquimod. The mean treatment time was 3.3 months and the mean follow-up after treatment was 5.5 months. Eight patients had a complete response to the medication and four had at least 75% regression of the lesions.[56]

Diaz-Arrastia *et al.* performed a chart review of eight patients with VIN, vaginal or cervical intraepithelial neoplasia to determine their clinical response to imiquimod cream. Treatment was three times weekly at bedtime, for six to 16 weeks. Four and two patients had complete and partial responses respectively.[57]

Case reports are described in three papers.[58-60]

Other Off-label Uses: Imiquimod was considered efficacious in the treatment of actinic cheilitis in a small trial (n=15) by Smith *et al.* Inflammatory reactions, however, were noted, with five patients showing local inflammation or edema.[61]

Other uses of imiquimod cream have been documented in case reports and series, including alopecia totalis, alopecia universalis,[62] bowenoid papulosis,[63,64] cutaneous extra-mammary Paget's disease,[65] cutaneous lymphoma,[66] discoid lupus erythematosus,[67] excised keloids,[68] granuloma annulare,[69] HPV-16-positive erythroplasia of Queyrat,[70] infantile hemangioma,[71] leishmaniasis,[72,73] lentigo maligna,[74] lip papillomatosis,[75] lip silicone granulomatous foreign body reaction,[76] keratoacanthoma,[77] melanomas,[78-82] porokeratosis of Mibelli[83] and stucco keratosis[84]