Imiquimod Cream: A New Multipurpose Topical Therapy for Dermatology

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Educational Objectives

- Review the literature on the reported uses of imiquimod in the treatment of a variety of skin diagnoses.
- Describe the antiviral properties of imiquimod.
- Differentiate between approved and unapproved clinical indications of imiquimod.

Introduction

Imiquimod (Aldara™, 3M Pharmaceuticals) is an imidazoquinoline amine that has been approved for use by the Food and Drug Administration (FDA) for external genital and perianal warts (condylomatum acuminatum). Sold as a 5% cream, imiquimod has demonstrated utility for treating dermatological diseases of both neoplastic and infectious etiology. Imiquimod is an immune response modifier that increases local cytokine production, with a subsequent activation of both the innate (rapid, nonspecific) and adaptive (specific, cellular, and humoral) immune systems. These characteristics have led to its application in a variety of dermatological conditions. This article reviews the reported uses of imiquimod in the treatment of various skin diseases.

When applied to the skin, imiquimod demonstrates antiviral potency. Regression of condylomatum acuminatum that has been treated with imiquimod is strongly correlated with a decrease in human papillomavirus (HPV) deoxyribonucleic acid (DNA) and messenger ribonucleic acid (mRNA) expression for viral proteins.[1] Interestingly, imiquimod has no antiviral effects *in vitro*;[2] rather, its mechanism of action is thought to stem from its effects on the immune system. Imiquimod induces peripheral monocytes and macrophages to release interferon α and interleukin (IL)-12. Both cytokines promote a cell-mediated immune response led by CD8+ cytotoxic T cells and natural killer cells.[3]

The antiviral properties of imiquimod may also stem from its ability to increase the serum concentration of (2'-5') oligoadenylate synthetase.[2] This capability appears to be necessary for some of the antiviral properties of interferon. One study reported that (2'-5') oligoadenylate synthetase levels increase in warts that have been treated with imiquimod.[1]

Imiquimod's effectiveness also relates to its action on Langerhans cells, the major antigen-presenting cells in the epidermis. Exposure to imiquimod induces human Langerhans cells to increase their presentation of antigens.[2] Studies in mice also show that imiquimod enhances the migration of Langerhans cells to draining lymph nodes, where these cells present antigen to T cells. Thus, it appears that imiquimod's effects on Langerhans cells might help to stimulate the body's adaptive immune response.[2]

Imiquimod also has antitumor activity, which might stem from the drug's ability to stimulate a cell-mediated immune response.[4] Application of imiquimod also leads to the release of IL-12, tumor necrosis factor α, and interferon α, which inhibit angiogenesis and increase cytotoxic T cells and natural killer cells.[3,5]

Imiquimod also up-regulates IL-2, which down-regulates IL-10, thus reversing the suppression of antitumor T cells.[6]

Clinical Indications

FDA-Approved Uses

Genital Warts

In 1997, the FDA approved topical imiquimod for use in external genital and perianal warts. The current edition of *Sexually Transmitted Diseases Treatment Guidelines—2002* recommends imiquimod cream 5% for external genital warts.[7]

The cream should be applied before bedtime three times weekly (e.g., Monday, Wednesday, and Friday) and should be washed off in the morning with soap and water for up to 16 weeks. In one multicenter, randomized, placebo-controlled, blind trial, 50% of patients using imiquimod in this manner were free of warts by 16 weeks, and a recurrence rate of only 13% was

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observed at follow-up 12 weeks later.[8] Most of the patients experienced mild to moderate local erythema, but imiquimod was generally well tolerated.

Imiquimod's utility for condylomatum acuminatum compares well with other common treatments. For example, studies report complete clearance rates of warts in 32% to 80% of patients receiving podophyllin (Podocon-25®, Paddock), 45% to 88% of those using podofilox (Condylox®, Oclassen) 69% to 79% of those undergoing cryosurgery, and up to 80% of those using bichloroacetic and trichloroacetic acids.[8] Published recurrence rates for these treatments are 60% to 65% with podophyllin, 19% with surgical excision, 22% with electrosurgery, and 21% with cryotherapy.[9]

Imiquimod and podofilox are the only two medications available for self-application by the patient at home.[8] In one study, however, imiquimod yielded a 39% greater sustained clearance rate than did podofilox gel, and it was 3% less costly for each successful outcome.[10]

Off-Label Uses

Nongenital Warts

Because imiquimod is effective against condylomatum acuminatum, dermatologists have attempted to treat other HPV-associated warts with this agent. One study described the use of 5% imiquimod for verruca vulgaris (common warts) located on the hands, face, trunk, and feet of 50 patients.[11] When imiquimod was applied for five consecutive days of the week for up to 16 weeks, 30% of patients achieved complete clearance of warts, with no recurrences observed in these patients at follow-up 32 weeks after treatment. Imiquimod was well tolerated in this study, and the investigators concluded that imiquimod was safe, painless, and effective for children. The authors also hypothesized that paring warts before treatment might improve efficacy by allowing the drug to penetrate the relatively thick stratum corneum, which typifies verruca vulgaris.

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Case reports also describe the success of imiquimod in treating recurrent verruca plana (flat warts). In one case, a 21-year-old woman was successfully treated with imiquimod for facial verruca plana that had been resistant to tretinoin cream, gel, and solution formulations; adapalene gel (Differin®, Galderma); 5-fluorouracil (Efudex®, ICN Pharmaceuticals); cryotherapy with liquid nitrogen; and oral cimetidine (Tagamet®, GlaxoSmithKline).[12]

Imiquimod therapy was also successful in a 42-year-old man who had been treated for warts that had been resistant to keratolytic agents, cryotherapy, excochleation, cimetidine, and dimepranolinosin.[13]

Lower-lip papilloma that had not responded to cryotherapy and interferon β was also successfully treated with imiquimod.[14] Imiquimod cream 5% has also been helpful in the treatment of plantar and periungual warts that have been covered by duct tape for occlusion.[15]

Molluscum Contagiosum

Imiquimod initiates a T helper (TH1), cell-mediated immune response and enhances the immune system's ability to fight viral infections. Physicians have recently documented the drug's utility in the treatment of molluscum contagiosum, caused by poxvirus. One study reported the use of imiquimod cream 5% for five consecutive days of the week for up to 16 weeks.[11] Of 15 patients treated this way, eight were free of lesions at the end of the study. Six of the seven children in the study had a complete response. Only one of the study's patients experienced a recurrence by the follow-up visit 10 weeks after achieving complete remission.

An analogue of the agent (imiquimod 1% in a cream-formulated base) has also been studied for the treatment of molluscum contagiosum. In a placebo-controlled, double-blind study, 100 men applied the cream or a placebo to lesions three times a day for five consecutive days per week.[16] By the end of four weeks, 82% of the imiquimod group but only 16% of the placebo group experienced complete resolution of the lesions. The drug was well tolerated, and only one patient who had been successfully treated with imiquimod experienced a relapse at follow-up 10 months later.

Three other case reports document the safety, efficacy, and ease of use of imiquimod for children with molluscum contagiosum.[17] Two other case reports have documented the ability of imiquimod cream 5%, used daily for several weeks, in treating refractory molluscum contagiosum in patients testing positive for human immunodeficiency virus (HIV) infection.[18,19]

Genital Herpes

Imiquimod has been shown to prevent primary infection in guinea pigs inoculated with herpes simplex virus (HSV) and to reduce the number of recurrences of HSV infection in guinea pigs.[20–23] These results have led physicians to try imiquimod for the treatment of genital herpes in humans. One case report describes a 34-year-old man with a five-year history of HIV infection who had genital herpes for five months.[24] Treatment with acyclovir, valcyclovir, and famcyclovir had been unsuccessful. Imiquimod 5% was applied three times per week, and after one month the patient was free of lesions. In another report, a 30-year-old woman with a two-year history of recurrent HSV infection had been treated in the past with acyclovir.[25] Treatment with imiquimod 5% three times per week was initiated, and her lesions cleared within three months. The lesions were still absent at follow-up six months after treatment.

Squamous Cell Carcinoma in Situ

Application of imiquimod leads to the release of cytokines that may be important in the treatment of squamous cell carcinoma (SCC)[4] and to the production of cytokines with antiangiogenic properties that may play a role in tumor inhibition.[26] One induced cytokine, interferon α, might also stimulate natural killer cells to have antitumor properties.[27] For these reasons, physicians have tested imiquimod's utility in treating SCC *in situ*.

In one phase II, open-label study, imiquimod 5% was applied daily to lesions on the legs, shins, and shoulders for up to 16 weeks.[28] Of the 16 treated patients, 87.5% were free of lesions by the study's completion and none of the 13 patients showed any evidence of tumor recurrence at a follow-up examination six months later. Most of the patients experienced local erythema within one week of treatment, and six patients stopped treatment

early because of local skin reactions. The investigators suggested altering the dosage schedule to temper skin reactions.

Treatment of SCC *in situ* in immunosuppressed patients has been described. For example, imiquimod 5% three times per week in conjunction with 5-fluorouracil four times per week has been used to treat SCC *in situ* in renal transplant recipients.[5] 5-Fluorouracil was used with imiquimod because its therapeutic index is increased when it is combined with interferon α, a cytokine induced by imiquimod.[29,30] All five patients treated in this way were free of lesions within four weeks and experienced no major side effects.

Another case report describes the use of 5% imiquimod three times per week and 5-fluorouracil three times per week in an HIV-positive patient with recurrent perianal and anal SCC *in situ*.[31] Within three weeks, the lesions had disappeared but HPV-positive tissue remained at the site of application.

Imiquimod has been used to treat head and neck SCC *in situ* in patients with chronic lymphocytic leukemia.[26] Leukemia in these patients causes an immunodeficiency with a shift from a TH1 to a TH2 cytokine pattern. All five subjects received imiquimod 5% three times a week, valcyclovir 1000 g/day (as prophylaxis against HSV), and sulindac (Clinoril®, Merck) 200 mg twice a day for up to 16 weeks. Biopsy findings at least five months after the completion of treatment demonstrated the absence of lesions in each patient, and most of the patients experienced minimal irritation from the treatment regimen.

Imiquimod has also been used to treat anogenital SCC *in situ*, which is associated with HPV. One case report describes a 47-year-old man with penile SCC *in situ* who applied imiquimod 5% daily for several weeks.[32] More than three months after treatment, the lesions were gone at follow-up.

In a different study, a 65-year-old man with penile SCC *in situ* applied imiquimod 5% once daily for 24 days, with a one-month holiday after the 11th day. The lesion cleared and was gone at follow-up 18 months after treatment.[6]

Imiquimod was used in the case of a 38-year-old woman with a history of bowenoid papulosis on the labia majora that had been refractory to treatment with laser therapy and podophyllin.[33] Her lesion resolved within eight weeks of initiating treatment with imiquimod 5% every other day or every day.

Imiquimod was also used to treat 13 women with a history of vulvar intraepithelial neoplasia (VIN) refractory to surgery, steroids, 5-fluorouracil, or podophyllin.[3] Only two of the 13 study participants could tolerate imiquimod 5% three times per week. Biopsy findings were negative for only three of the 13 patients on follow-up, but koilocytosis (abnormal cells) remained.

Physicians have reported the elimination of recurrent grade 3 (VIN 3) in four of four women treated with imiquimod 5% three times per week.[34] Three of the four women, however, experienced recurrences during follow-up biopsy.[34]

Imiquimod has also been used outside of the dermatological realm for the treatment of high-grade vaginal intraepithelial neoplasia (VAIN) and cervical intraepithelial neoplasia (CIN). In one study, two women with a history of CIN and two with a history of VAIN who had not responded to earlier surgical resection were given imiquimod 5% for use three times per week for up to 16 weeks.[35] One of the women with CIN showed a complete response but suffered a local recurrence. A complete response was also seen in one of the women with VAIN, and the biopsy results at follow-up were negative at 40 months after treatment.

In another study of three women with grade 2 or 3 VAIN, imiquimod 5% was applied under colposcopic guidance three times a week for eight weeks.[36] After eight weeks of treatment, biopsy findings showed that grade 3 VAIN in two women had regressed to grade 1; grade 2 VAIN in one woman had completely regressed. Histological findings showed that HPV infection also remained completely regressed.

Basal Cell Carcinoma

The properties of imiquimod lead to the release of cytokines that may be important for treating cutaneous basal cell carcinomas.[4] One randomized, double-blind, placebo-controlled trial demonstrated a complete response rate of 83% when imiquimod 5% was applied to superficial and nodular basal cell carcinoma lesions.[4] This rate approached that of surgical treatment.[4]

In another phase II dose–response, open-label trial, imiquimod 5% was found to be most effective when it was applied daily for six weeks.[37] When treatment was carried out in this way, 88% of superficial basal cell carcinoma lesions completely regressed and side effects were tolerable.

Unfortunately, neither of these studies documented the treatment of high-risk basal cell carcinomas, including facial, perirorificial, morpheaform, sclerosing, and micronodular cancers.

Actinic Keratosis

Actinic keratoses, which are precancerous lesions, have also been treated with imiquimod. In one study, imiquimod 5% was applied to actinic keratosis on the heads of six patients three times per week for up to eight weeks.[27] The lesions in all six patients resolved, and no recurrences were noted on follow-up examination at least 12 months after treatment. All patients experienced local erythema; however, compared with the use of 5-fluorouracil, imiquimod caused less discomfort and led to a better cosmetic appearance. Further studies are needed to see whether treating actinic keratosis with imiquimod might be able to reduce the incidence of SCC.

Melanoma

An 88-year-old woman with lentigo maligna on her forehead was treated with 5% imiquimod both three times weekly and daily for five months.[38] Biopsy findings at that time were negative, and there was no recurrence at nine months after clearance of the lesion. In another case, a 50-year-old woman with disseminated cutaneous metastatic melanoma had been treated with dacarbazine (DTIC-Dome®, Bayer) without success.[39] After 12 weeks of imiquimod 5% applications three times weekly to the lesion, the tissue appeared normal after biopsy.[39] Six weeks after treatment, pathological examination confirmed complete regression of the original lesion.[39]

Porokeratosis of Mibelli

A 55-year-old man with porokeratosis of Mibelli (crater-like patches with an elevated, thick border) was prescribed imiquimod cream 5% once daily for five consecutive days per week.[40] After three months, the lesion had not resolved. Treatment was continued with instructions to apply adhesive polyethylene dressing over the lesion after application of imiquimod. The

lesion resolved in five weeks, and no recurrence was observed with biopsy one year after treatment.

Cutaneous Leishmaniasis (Skin Ulcers)

Imiquimod stimulates macrophages to release nitric oxide, which destroys *Leishmania* amastigotes (Leishman-Donovan bodies) *in vitro*.[41] Imiquimod has also been useful in the treatment of experimentally induced cutaneous leishmaniasis in mice.[41] These results have encouraged physicians to test the efficacy of imiquimod for cutaneous leishmaniasis in humans.[42]

One study described the treatment of 12 patients from Peru with cutaneous leishmaniasis.[42] Standard therapy with meglumine antimonate had been unsuccessful for all of the patients. Therapy was restarted with intramuscular (IM) meglumine antimonate daily for 20 days in addition to imiquimod cream 5%, which was applied daily for 20 days. The therapy was well tolerated, and the lesions resolved in six of the 12 patients by the end of treatment. In the other six patients, the lesions improved or were entirely resolved at two to four months after treatment. By six months after treatment, only one of 10 patients still being monitored had experienced a recurrence. Thus, the cure rate at the six-month follow-up was approximately 90%. This number is encouraging, because only about 25% of those who do not respond initially to meglumine antimonate therapy respond to a second trial of meglumine antimonate.[42]

Other Dermatological Conditions

Tattoos. In a study that evaluated isotretinoin, imiquimod, or both for removal of tattoos in guinea pigs, imiquimod alone was found to be the more effective agent.[43] Imiquimod cream 5% was applied to one set of guinea pigs six hours after an application of tattoo ink. The imiquimod applications were continued every six hours for seven days. At 28 days after the initiation of treatment, the pigment was barely perceptible on microscopy but inflammation and fibrosis were observed. More research is needed to see whether mature tattoos can also be removed by imiquimod.

Alopecia. Alopecia (hair loss) is another condition that might respond to imiquimod because other chemicals that also elicit a cell-mediated immune response have successfully treated the disease.[44]

T-cell lymphoma. Some physicians also foresee the usefulness of imiquimod for cutaneous T-cell lymphoma, which has already been shown to be treatable with interferon α, a cytokine induced by imiquimod.[45]

Atopic dermatitis. This inflammatory condition may be amenable to immune modification via treatment with imiquimod. Lymphocytes in patients with atopic dermatitis release cytokines with a TH2 profile, and some dermatologists anticipate that imiquimod might be able to relieve this condition by restoring a TH1 cytokine profile.[44]

Keloids. Anecdotal evidence suggests that imiquimod might hold promise as a postsurgical treatment for keloids to help prevent recurrences.[46]

Infantile hemangiomas. A recent report suggests that imiquimod might be useful for the treatment of these vascular tumors.[47]

Adverse Reactions

From the literature reviews[1–47] and the *Physicians' Desk Reference* information[48] on imiquimod, the major limitation to the use of this medication is the occurrence of local cutaneous side effects. Reactions at the application site have included patients' complaints of itching, burning, pain, and soreness.[48] Localized cutaneous reactions have included erythema, erosion, flaking, induration, ulceration, scabbing, and vesicle formation.[48] In rare instances, systemic side effects of headache, influenza-like symptoms, and myalgia have developed.[48]

In our clinical practice, we find that decreasing the frequency of applications and using a bland emollient cream, as needed, often facilitate completion of the therapy. We avoid the use of topical steroids because they would inhibit the desired effect of imiquimod.

Conclusion

Imiquimod cream has been used widely in both infectious and neoplastic cutaneous and mucocutaneous processes. Physicians and pharmacists should be aware of alternative off-label uses of this medication. Imiquimod is a new, unique, and painless alternative for patients, with the only major complaint usually being just local irritation. This minor result should allow physicians to prescribe imiquimod in sensitive patients as well as in candidates who are not suitable for surgery. The off-label uses, unfortunately, vary in their evidence-based status. Additional placebo-controlled, randomized, and double-blind clinical trials are needed to confirm and elaborate the utility of imiquimod in several of the diseases discussed in this article. According to a recent survey of drugstore.com, 12 packets of Aldara™ cream 5% cost approximately $127.[49]

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Disclosure

Dr. English and Mr. Najarian have indicated that they have no commercial relationships to disclose. This article contains information on unapproved uses.

Continuing Education Examination for Pharmacists

TOPIC: **Imiquimod Cream: A New Multipurpose Topical Therapy for Dermatology**

CE Evaluation: Select the one best answer to each of the following questions, and record your response on the examination answer sheet. Complete additional requested information. Forward the answer sheet, with appropriate payment, to the Office of Health Policy and Clinical Outcomes, Thomas Jefferson University Hospital, at the address indicated. A certificate of completion will be mailed within three weeks of receipt of exam/payment. (A minimum test score of 70% is required.)

Multiple Choice

Select the one correct answer.

1. The use of imiquimod is approved by the FDA for:
- **a.** condylomatum acuminatum.
- **b.** verruca plana.
- **c.** molluscum contagiosum.
- **d.** actinic keratosis.

2. Which of the following statements is *false*?
- **a.** Imiquimod has no antiviral effects *in vitro*.
- **b.** Imiquimod has no antiviral potency when it is applied to the skin.
- **c.** Imiquimod has the ability to stimulate a cell-mediated immune response.
- **d.** Imiquimod increases local cytokine production.

3. Which of the following statements is *false*?
- **a.** Imiquimod is an imidazoquinoline amine.
- **b.** Imiquimod is an immune response modifier.
- **c.** Imiquimod has been shown to reverse the suppression of antitumor T cells.
- **d.** Imiquimod promotes angiogenesis and decreases cytotoxic T cells and natural killer cells.

4. Regression of condylomatum acuminatum treated with imiquimod is strongly correlated with an increase in human papillomavirus (HPV) deoxyribonucleic acid (DNA) and messenger ribonucleic acid (mRNA) expression for viral proteins.
- **a.** True
- **b.** False

5. This article mentions that imiquimod is safe, painless, and effective for off-label treatment of children with:
- **a.** common warts (verruca vulgaris).
- **b.** papilloma of the lower lip.
- **c.** genital herpes (herpes simplex virus [HSV]).
- **d.** actinic keratosis.

6. According to the placebo-controlled, double-blind study of 100 men treated for molluscum contagiosum, which formulation of imiquimod was used?
- **a.** imiquimod 10% solution
- **b.** imiquimod 5% cream covered with duct tape
- **c.** imiquimod 1% in a cream-formulated base
- **d.** imiquimod 0.1% cream covered with duct tape

7. When used off-label for genital herpes (HSV), several case reports show that imiquimod has some activity against HSV previously treated with acyclovir.
- **a.** True
- **b.** False

8. According to this article, 5-fluorouracil is used with imiquimod for the off-label treatment of squamous cell carcinoma *in situ* because of evidence that:
- **a.** imiquimod decreases the effects of 5-fluorouracil by inhibiting cytokines.
- **b.** imiquimod induces interferon α, which increases the therapeutic index of 5-fluorouracil.
- **c.** imiquimod is better tolerated than 5-fluorouracil.
- **d.** imiquimod causes less local irritation with 5-fluorouracil.

9. Which is *not* a major limiting factor in the use of imiquimod?
- **a.** the occurrence of gastrointestinal side effects: nausea, vomiting, diarrhea
- **b.** the occurrence of systemic side effects: headache, influenza-like symptoms, myalgia
- **c.** the occurrence of local cutaneous side effects: erythema, erosion, ulceration, scabbing
- **d.** the fact that only tattoos less than six hours old are eligible for removal

10. Which of the following processes was *not* mentioned in this article as having a potential treatment benefit from the use of imiquimod cream?
- **a.** neoplastic cutaneous processes
- **b.** mucocutaneous processes
- **c.** infectious cutaneous processes
- **d.** musculoskeletal processes

Continuing Education for Pharmacists Examination Answer Sheet

TOPIC: **Imiquimod Cream: A New Multipurpose Topical Therapy for Dermatology**

P&T® 2003;28(2):122–126.

Program #079-999-03-014-H01
Expiration Date: February 28, 2004

Complete this answer sheet (including the questions and information requested below), detach, and mail to:

Office of Health Policy and Clinical Outcomes
Thomas Jefferson University Hospital
attn: Continuing Pharmacy Education
1015 Walnut St, Suite 115
Philadelphia, PA 19107

Directions

Select the one best answer to each question and darken the appropriate circle.

1. (a) (b) (c) (d)
2. (a) (b) (c) (d)
3. (a) (b) (c) (d)
4. (a) (b) (c) (d)
5. (a) (b) (c) (d)
6. (a) (b) (c) (d)
7. (a) (b) (c) (d)
8. (a) (b) (c) (d)
9. (a) (b) (c) (d)
10. (a) (b) (c) (d)

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(Circle the appropriate response):

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Applicability to practice	1	2	3	4	5
Objectives met	1	2	3	4	5
Ease of comprehension	1	2	3	4	5

Time (in hours) to read the article and complete the exam:

_____

Suggested topics for future consideration:

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I certify that I have completed this course independently:

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Date Completed _____

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Continuing Medical Education for Physicians

TOPIC: Imiquimod Cream: A New Multipurpose Topical Therapy for Dermatology

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Title: **Imiquimod Cream: A New Multipurpose Topical Therapy for Dermatology**
Authors: **David J. Najarian, BS, and Joseph C. English III, MD**
Submission deadline: **February 28, 2004**

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Time needed to complete this CME activity: ☐ < 1 hr ☐ 1 hr

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Signature (required)

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(very effective) (not at all effective)

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3. Which of the following best describes a change you might consider making in your practice as a result of something you learned from this activity? (Please circle only one response.)
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   B. Make a major change in what I currently do.
   C. Follow a procedure, use a technique/technology that is completely new to me.
   D. Follow a procedure, use a technique/technology that I currently use but for a different purpose.
   E. None of the above, but some change.
   F. Not considering any changes.

4. Please describe any change(s) you plan to make in your practice as a result of this activity: _____

_____

_____

5. How committed are you to making these changes? 5 4 3 2 1
(very committed) (not at all committed)

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