Issue 61
September 2004

Issues in Emerging Health Technologies

Imiquimod 5% Cream for Actinic Keratosis

Summary

- ✓ **Imiquimod 5% cream has been available since 1997 for the treatment of genital warts. Health Canada has expanded the indication to include actinic keratosis (AK).**
- ✓ **There are no trials comparing imiquimod 5% cream to standard AK therapy; placebo-controlled trials have shown an increased lesion clearance rate of 30% to 55% eight weeks post-treatment.**
- ✓ **Side effects include local skin reactions that can be severe and require discontinuation of treatment in 2% to 4% of patients.**
- ✓ **Imiquimod has shown a great potential for use in unapproved indications.**

The Technology

Imiquimod, an imidazoquinoline, modifies innate and cell-mediated immune responses by stimulating immune system cells such as natural killer cells and antigen-presenting cells; and by inducing cytokines such as interferon alpha, tumour necrosis factor alpha and interleukin 1, 6, 8, 10 and 12.[1,2] These responses eliminate viral infections and tumours.[3] Imiquimod's antitumour effect has been tested in clinical trials for oncological lesions including AK, squamous and basal cell carcinomas.[4]

Regulatory Status

Available since 1997, imiquimod 5% cream (Aldara™, 3M Pharmaceuticals) is indicated for the treatment of external genital and perianal warts (condylomata acuminata) in adults.[5] On June 24, 2004, Health Canada issued a Notice of Compliance for imiquimod 5% cream for the treatment of AK in adults.[6] In the US, imiquimod was approved for the treatment of AK in March 2004.[7]

Health Canada is considering a request for expansion of the current indications to include superficial basal cell carcinoma (Mr. David Marsh, 3M Pharmaceuticals, London, ON: personal communication, 2004 July 12).

Patient Group

AK, which is also called solar keratosis or squamous cell carcinoma (SCC) in situ, is a skin condition characterized by red and scaly lesions most often found on sun-exposed areas such as the head, neck, forearms and dorsum of the hands. A diagnosis is made through clinical history and physical examination. A biopsy may be required to verify the diagnosis or to exclude cancer.[8]

The development of AK is associated with individual susceptibility (i.e., fairness of skin), cumulative ultraviolet radiation exposure and advancing age. The American Academy of Dermatology estimates that 60% of the individuals at risk will have at least one AK lesion after the age of 40.[8] From 20% to 70% of lesions that tend to be thinner regress on their own over one to two years, while 15% of lesions recur.[9]

It is difficult to clinically differentiate thicker AK lesions from SCC. As a result, a biopsy may be needed to confirm the diagnosis.[10] One longitudinal study shows that the risk of an AK lesion transforming into SCC within a year is less than 1:1000.[11] For individuals with multiple AK lesions, this involves a lifetime risk of 6% to 10%.[12]

SCC shares the same risk factors as AK. Its greatest risk factor is the presence of AK lesions or a history of non-melanoma skin cancer.[12] Not all SCC arise from AK lesions, however, as 40% of SCC comes from previously normal skin. Whether it is cost-effective to treat all AK lesions to prevent SCC is unknown.[13]

Current Practice

The treatment of AK involves surgical or non-surgical interventions or a combination of both. The choice of treatment is based on the patient's medical status, lesion characteristics (number, size, anatomical location and growth pattern) and previous treatment.[8]

Cryosurgery and curettage are used to treat small areas with few lesions. Neither cryosurgery nor curettage has been evaluated in randomized controlled trials against placebo or other treatments.[9,14]

Fluorouracil is used when treating numerous lesions covering a large area. In Canada, it is commercially available as a 5% cream (Efudex™, Valeant Pharmaceuticals).[5]

Fluorouracil has been tested alone or in combination in non-randomized, unblinded comparative studies.[15] Common dermatological adverse events may limit its use.[16]

Other treatments include chemical peels, dermabrasion, laser therapy, excision and photodynamic therapy.[8,17]

Trial	Areas Treated	Treatment	Results (% patients)
Chen K *et al.*, 2003 [19]	5 to 15 AK lesions located on scalp, forehead or cheeks	imiquimod 5% cream (n=29) or vehicle cream (n=10) applied to one treatment area 3x/week for 3 weeks followed by 4-week rest; treatment cycle repeated once in patients with <75% clearance of lesions	≥75% clearance§ imiquimod=72.4% placebo=30.0% p=0.027
†Edwards L *et al.*, 2000 [20]	at least 3 AK lesions of ≥0.5 cm in diameter	vehicle cream (n=14) or imiquimod 5% cream applied to 3 untreated lesions 2x/day (n=2) or 1x/day (n=17) or 3x/week (n=4) or 1x/week (n=4) until lesions cleared or for 16 weeks	Complete resolution of 3 target lesions§ imiquimod=37.0% placebo=7.1% p=not reported
†Korman N *et al.*, 2004 [21] Study 1 and †Jorizzo J *et al.*, 2004 [22] Study C	4 to 9 AK lesions within contiguous 25 cm^2 treatment area on face or balding scalp but not both	imiquimod 5% cream (n=117) or vehicle cream (n=124) applied 3x/week for 16 weeks; rest period allowed at discretion of investigator	Complete clearance rate at 8 weeks post-treatment§ imiquimod=47.9% placebo=8.1% p<0.001
†Korman N *et al.*, 2004 [21] Study 2 and †Jorizzo J *et al.*, 2004 [22] Study D	4 to 9 AK lesions within contiguous 25 cm^2 treatment area on face or balding scalp but not both	imiquimod 5% cream (n=125) or vehicle cream (n=126) applied 3x/week for 16 weeks; rest period allowed at discretion of investigator	Complete clearance rate at 8 weeks post-treatment§ imiquimod=40.8% placebo=6.3% p<0.001
†Korman N *et al.*, 2004 Study 3 [21] †Jorizzo J *et al.*, 2004 [22] Study E	4 to 9 AK lesions within contiguous 25 cm^2 treatment area on face or balding scalp but not both	imiquimod 5% cream (n=147) or vehicle cream (n=139) applied 3x/week for 16 weeks	Complete clearance rate at 8 weeks post-treatment* imiquimod=57.1% placebo=2.2% p<0.001
Lebowl M *et al.*, 2004 [23] †Jorizzo J *et al.*, 2004 [22,24] Study A and Study B	4 to 9 AK lesions within contiguous 25 cm^2 treatment area on face or balding scalp but not both	imiquimod 5% cream (n=215) or vehicle cream (n=221) applied 2x/week for 16 weeks	Complete clearance rate at 8 weeks post-treatment§ imiquimod=45.1% placebo=3.2% p<0.001
Stockfelth E *et al.*, 2002 [25]	3 to 10 AK lesions of ≤20 cm^2 located on head, forearm or hand and confirmed with biopsy	imiquimod 5% cream (n=25) or vehicle cream (n=11) at night 3x/week until lesions cleared or for 12 weeks; weekly applications decreased if severe adverse reactions occurred	Complete clinical clearance at 2 weeks post-treatment* imiquimod=84.0% (95% CI: 64% to 95%) placebo=0% p<0.001

†available as a poster only; *biopsy confirmed; §clinically confirmed. Complete clearance rate means no clinically visible lesions in treatment area.

The Evidence

Eight randomized, double-blind, placebo-controlled trials were conducted. The studies lasted ≤16 weeks. In one study, post-treatment follow-up visits were conducted to clinically assess long-term clearance. At 24 months, 18% of patients had new AK lesions.[18] More evidence on the reduction of late recurrences is needed.

Adverse Effects

Adverse drug reactions reported in clinical trials were mainly local skin reactions such as erythema, erosion, excoriation, flaking, burning, hyperpigmentation, hypopigmentation, pruritis or edema.[19-21,25] These reactions can be severe and require a rest period in up to 40% of patients or discontinuation of treatment in 2% to 4% of patients.[21,26] Although imiquimod is minimally absorbed through the skin,[5,27] systemic side effects including headache, influenza-like symptoms and myalgia have been reported.[28] Drug-induced pemphigus was seen in one patient.[29]

Administration and Cost

Imiquimod 5% cream is patient-administered. It is available as single-use packets, each containing 250 mg of cream. An area of 20 cm^2 will require one packet.[5] A box containing 12 packets costs $137.[30]

The frequency and duration of application that provide the best efficacy has not yet been determined. Assuming twice weekly applications for 16 weeks, one course of treatment will require three boxes at a cost of $411.

Concurrent Developments

Researchers have studied the use of imiquimod cream in over 25 dermatological conditions including basal cell carcinoma, SCC, molluscum contagiosum and non-genital warts. Few studies are randomized controlled trials.[31]

Other treatments of AK that are being investigated include retinoid therapy and intralesional interferon.[17]

Rate of Technology Diffusion

An American survey conducted by 3M Pharmaceuticals in 2000 showed that AK was the reason for 6.1% of all imiquimod prescriptions. The remaining prescriptions were for genital warts (13.1%) and unapproved indications.[32] Decision-makers should be aware of the potential for use in unapproved indications.

Implementation Issues

It is difficult to determine what lesions will become SCC, as not all SCC arise from AK lesions. Thicker AK lesions must be treated to prevent SCC and to relieve symptoms.[8]

Randomized trials have shown that imiquimod, when compared with placebo, is effective in inducing clearance of lesions in 30% to 55% of patients. Like its comparator, fluorouracil cream, its main advantage is that it can be patient-administered.

Imiquimod 5% cream has not been compared to other standard AK treatments. Future research is needed to determine its place in therapy; the ideal frequency and duration of application; and its long-term effectiveness.

References

1. Marini M. *Int J Dermatol* 2002;41 Suppl 1:1-2.
2. Berman B. *Int J Dermatol* 2002;41 Suppl 1:7-11.
3. Rigel D, et al. *Acta Derm Venereol Suppl* 2003;(214):5-7.
4. Stanley MA. *Clin Exp Dermatol* 2002;27(7):571-7.
5. *CPS: compendium of pharmaceuticals and specialties.* 38th ed. Ottawa: Canadian Pharmacists Association; 2003.
6. *Notices of compliance: prescription products for human use: January 1 - July 2, 2004* [monograph online]. Ottawa: Therapeutics Product Directorate, Health Canada; 2004. Available: http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/noc/2004/pre2004et.txt

7. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. *NDA 20-723/S-015 [FDA approval letter]*. Rockville (MD): The Center; 2004 Mar 2.
8. Drake LA, et al. *J Am Acad Dermatol* 1995;32(1):95-8.
9. Managing solar keratoses. *Drug Ther Bull* 2002;40(5):33-5.
10. Moy RL. *J Am Acad Dermatol* 2000;42(1 Pt 2):S8-S10.
11. Marks R, et al. *Lancet* 1988;1(8589):795-7.
12. Salasche SJ. J *Am Acad Dermatol* 2000;42(1 Pt 2):S4-S7.
13. Marks R. *Arch Dermatol* 1991;127(7):1031-3.
14. New treatments for actinic keratoses. *Med Lett Drugs Ther* 2002;44(1133):57-8.
15. Tutrone WD, et al. *Cutis* 2003;71(5):365-70.
16. Silapunt S, et al. *Semin Cutan Med Surg* 2003;22(3):162-70.
17. Jeffes EWB, et al. *Am J Cancer* 2003;2(3):151-68.
18. Stockfleth E, et al. Presentation at 62nd Annual Meeting of the American Academy of Dermatology; 2004 Feb 6; Washington. Abstract no P469. Available: http://www.aad.org/abstracts.pdf.
19. Chen K, et al. *Australas J Dermatol* 2003;44(4):250-5.
20. Edwards L, et al. Presentation at 58th Annual Meeting of American Academy of Dermatology; 2000 Mar 10; San Francisco.
21. Korman N, et al. Presentation at 62nd Annual Meeting of the American Academy of Dermatology; 2004 Feb 6; Washington. Abstract no P475. Available: http://www.aad.org/abstracts.pdf.
22. Jorizzo J, et al. Presentation at 62nd Annual Meeting of the American Academy of Dermatology; 2004 Feb 6; Washington. Abstract no P488. Available: http://www.aad.org/abstracts.pdf.
23. Lebwohl M, et al. *J Am Acad Dermatol* 2004;50(5):714-21.
24. *3M submits supplemental new drug application to FDA for Aldara™ (Imiquimod) cream, 5% for the treatment of actinic keratosis [news release]*. St. Paul (MN): 3M; 2003 May 5. Available: http://www.3m.com/us/healthcare/pharma/sNDA.jhtml.
25. Stockfleth E, et al. *Arch Dermatol* 2002;138(11):1498-502.
26. Richwald GA. *Drugs Today (Barc)* 1999;35(7):497-511.
27. Owens ML, et al. *Prim Care Update Ob/Gyns* 1998;5(4):151.
28. Holdiness MR. *Contact Dermatitis* 2001;44(5):265-9.
29. Campagne G, et al. *Eur J Obstet Gynecol Reprod Biol* 2003;109(2):224-7.
30. 3M Pharmaceuticals. In: *PPS Pharma Publication.* Moncton (NB): Total Pricing System; 2003. p.21-6.
31. *Imiquimod cream: place in therapy* [monograph online]. Ottawa: The Canadian Coordinating Office for Health Technology Assessment; 2003. Pre-assessment no 22. Available: http://www.ccohta.ca/publications/pdf/No22_imiquimod_preassess.pdf.
32. Dahl MV. *J Am Acad Dermatol* 2002;47(4 Suppl):S205-S208.

This brief was prepared by
Christine Perras, B.Sc. Phm MPH, CCOHTA

CCOHTA takes sole responsibility for this bulletin, but we appreciate comments from the following reviewers:

Ronald Vender, MD FRCPC
Assistant Clinical Professor of Medicine
McMaster University
Hamilton ON

Stewart Adams, MD FRCPC
Divisional Head of Dermatology
University of Calgary
Calgary AB

Jeff Scott, MBChB MHSc MHSA FRCPC
Chief Medical Officer of Health
Nova Scotia Department of Health
Halifax NS

ISSN 1488-6324 (online)
ISSN 1488-6316 (print)
PUBLICATIONS MAIL AGREEMENT NO: 40026386
RETURN UNDELIVERABLE CANADIAN ADDRESSES TO
CANADIAN COORDINATING OFFICE FOR
HEALTH TECHNOLOGY ASSESSMENT
600-865 CARLING AVENUE
OTTAWA ON K1S 5S8