Effectiveness of Imiquimod Cream 5% for Treating Childhood Molluscum Contagiosum in a Double-blind, Randomized Pilot Trial

Amy U. Theos, MD; Rebecca Cummins, MD; Nanette B. Silverberg, MD; Amy S. Paller, MD

The safety and effectiveness of imiquimod cream 5% were evaluated in the treatment of molluscum contagiosum (MC) in children. Twenty-three children ranging in age from 1 to 9 years with MC infection were randomized to either imiquimod cream 5% (12 patients) or vehicle (11 patients). Parents applied study drug to patient's lesions 3 times a week for 12 weeks. Patients presented to the clinic every 2 weeks until the end of study (week 12) for safety evaluation and lesion count. Local skin reactions, partial and complete clearances, and lesion counts were statistically analyzed. Partial clearance (≥30% clearance of lesions) at weeks 4 and 12 was noted in 58.3% (7/12) and 66.7% (8/12) of imiquimod patients and in 0% (0/11) and 18.2% (2/11) of vehicle patients (imiquimod vs vehicle: week 4, P=.0046; week 12, P=.0361). Complete clearance at week 12 was noted in 33.3% (4/12) of imiquimod patients and in 9.1% (1/11) of vehicle patients. The mean percentage change in lesion count at week 12 was −45.9% in the imiquimod group and +26.9% in the vehicle group. Imiquimod was well tolerated and appears to be a promising therapeutic option in the treatment of MC in children. Larger studies are needed to confirm the results of this small pilot study.

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Molluscum contagiosum (MC) is a common cutaneous viral infection in children caused by the MC virus (MCV), a large, double-stranded DNA virus belonging to the poxvirus family. Lesions are usually small dome-shaped papules that often show a central umbilication.[1] Although MC lesions can involve any anatomic site in children, the most common locations include the trunk, axillae, antecubital and popliteal fossae, and crural folds.[2] The mode of transmission is thought to involve either direct contact with an infected individual or fomites. The incubation period and clinical course of MC are poorly documented.[3,4] In many immunocompetent patients, MC lesions eventually resolve spontaneously. However, the time course can range from months to years. Although spontaneous resolution occurs, persistent lesions, autoinoculation, associated eczematous dermatitis, scarring at the lesion site, and the risk for transmission to contacts justify active treatment.[5]

No drug therapies have been approved for the treatment of MC. Current treatment options include physical ablation, such as curettage and cryotherapy; chemical ablation with the vesicant cantharidin, podophyllin resin, silver nitrate, potassium hydroxide, or phenol; oral cimetidine; and no treatment.[6-12] Physical and chemical ablations often are associated with substantial pain, scarring, and frequent recurrences. Therefore, an alternative treatment would be highly desirable in pediatric patients.

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Dr. Theos is from the Departments of Dermatology and Pediatrics, University of Alabama Medical School, Birmingham. Drs. Cummins and Paller are from the Departments of Pediatrics and Dermatology, Northwestern University Medical School, Chicago, Illinois. Dr. Silverberg is from the Departments of Dermatology and Pediatrics, St. Luke's-Roosevelt Medical Center, New York, New York.

Dr. Paller is a consultant for 3M Pharmaceuticals. The other authors report no conflict of interest.

Reprints: Amy S. Paller, MD, Children's Memorial Hospital Center, 2300 Children's Memorial Plaza, #107, Chicago, IL 60614 (e-mail: apaller@northwestern.edu).

Imiquimod cream 5% is approved for the treatment of external genital warts in patients as young as 12 years. Imiquimod enhances the immune response against virus-infected cells, resulting in the activation of antigen-presenting cells, and later, T lymphocytes.[13] Due to its unique mechanism of action, topical imiquimod also has been used off-label in children for many dermatologic conditions, including MC and common warts, and appears to be well tolerated.[6,14-17]

Despite the increasing number of anecdotes, no placebo-controlled data have been published regarding the safety and efficacy of imiquimod cream for the treatment of MC. Thus, a 12-week, randomized, vehicle-controlled pilot study was conducted in children ranging in age from 2 to 11 years to evaluate the safety and efficacy of imiquimod cream for the treatment of MC.

Patients and Methods

Patients—After approval by the hospital institutional review board, children ranging in age from 2 to 11 years with MC involving less than 20% body surface area were enrolled in the study. Informed consent was obtained from the parents of all participants.

Study Design—This was a randomized, double-blind, vehicle-controlled pilot study to evaluate the safety and efficacy of imiquimod cream 5% in children with MC. Prospective study participants were screened by lesion involvement of less than 20% body surface area, immune status, presence of other concomitant skin disorders involving the intended application site, and hypersensitivity to imiquimod or any components of the vehicle. None of the female patients had started menses yet.

Eligible patients were randomized to either imiquimod or vehicle. Parents applied the contents of 1 packet to the patient's lesions 3 times a week for 12 weeks, using a maximum of 12.5 mg of study drug per dose. Each dose of study drug was applied just before normal sleeping hours and remained on the skin for approximately 8 to 10 hours before being washed off with soap and water.

Patients presented to the clinic every 2 weeks after treatment initiation. At each clinic visit, local skin reactions were assessed, lesion numbers were counted, and photographs were taken.

Statistical Analysis—All primary safety and efficacy analyses comparing imiquimod-treated and vehicle-treated patients used the intent-to-treat population. For the primary efficacy analysis end point (complete clearance rates), the 2-sided Fisher exact test was used. For the primary and secondary safety end points (physician-assessed and patient-assessed local skin reactions, respectively), the Wilcoxon rank sum test was used. Patients who missed clinic visits were considered nonresponders (ie, failures for complete and partial clearance analysis). For secondary efficacy end points, the

Table 1.

Patient Demographics

Variable	Treatment Group: Imiquimod, n (%) (n=12)	Treatment Group: Vehicle, n (%) (n=11)	Total, n (%) (N=23)
Sex			
Female	5 (41.7)	6 (54.5)	11 (47.8)
Male	7 (58.3)	5 (45.4)	12 (52.2)
Age, y			
Mean±SD	4.73±2.07	4.7±1.75	4.71±1.88
Range	1–9	2–8	1–9
Baseline lesion count			
Mean±SD	27.0±14.4	19.4±12.3	23.3±13.7
Range	10–60	5–45	5–60

Wilcoxon rank sum test and *t* test were used. All tests were performed at the 0.05 significance level.

Results

Patient Characteristics—A total of 23 patients were randomized to study drug: 12 patients received imiquimod, and 11 patients received vehicle. Two vehicle patients discontinued treatment at week 2, before lesion and safety assessments, for a total of 21 patients who completed the study. Of the 23 patients, 52.2% (12) were male. Age range was from 1 to 9 years, with a mean of 4.7 (±1.9) years (Table 1). Overall, the number of MC lesions at baseline ranged from 5 to 60, with a mean of 23.3 (±13.7).

Efficacy—Partial clearance was defined as at least a 30% decrease from baseline lesion count. At week 4, 58.3% (7/12) of imiquimod patients were partially cleared of MC lesions compared with none of the vehicle patients (*P*=.0046, 2-sided Fisher exact test)(Table 2). By weeks 8 and 12, 66.7% (8/12) of imiquimod patients were partially cleared compared with 18.2% (2/11) of vehicle patients (*P*=.0361, 2-sided Fisher exact test).

Beginning at week 4, a difference in the complete clearance of MC in the 2 treatment groups was observed (Table 2), though not statistically significant. By week 12, 33.3% (4/12) of imiquimod patients and 9.1% (1/11) of vehicle patients were completely cleared (Figure 1).

The percentage of baseline MC lesions decreased in the imiquimod group and increased in the vehicle group during the course of the study (Figure 2 and Table 2). Specifically, at week 12, a 45.9% decrease in the percentage of baseline MC lesions on average in the imiquimod group and a mean increase of 26.9% in the vehicle group were noted. An analysis of the number of lesions cleared per patient indicated that there was a significant difference to treatment end point (*P*=.03) in the mean number of lesions cleared per patient in both imiquimod and vehicle groups

Table 2.

Partial and Complete Lesion Clearances by Week

	Study Week	Mean Change From Baseline, %†	Median Clearance, %‡	Complete Clearance, n (%)	Partial Clearance, n (%)§	*P* Value*	
						Complete Clearance	Partial Clearance
Imiquimod	2	−6.1	0.0	0	3 (25)	—	.22
(n=12)	4	−29.7	32.7	2 (16.7)	7 (58.3)	.48	.005
	6	−40.1	40.0	3 (25)	6 (50)	.22	.07
	8	−46.2	56.0	4 (33.3)	8 (66.7)	.09	.04
	12	−45.9	45.9	4 (33.3)	8 (66.7)	.32	.04
Vehicle	2	10.6	−4.8	0	0		
(n=11)	4	13.0	−12.5	0	0		
	6	6.3	−11.1	0	1 (9.1)		
	8	2.3	−6.3	0	2 (18.2)		
	12	26.9	6.7	1 (9.1)	2 (18.2)		

*Treatment comparison was based on a 2-sided Fisher exact test.
†A negative percentage change indicates the percentage of the number of lesions cleared compared with baseline number of lesions.
‡A positive median percentage indicates an increase in lesion clearance.
§Partial clearance was defined as at least a 30% decrease from baseline lesion count.

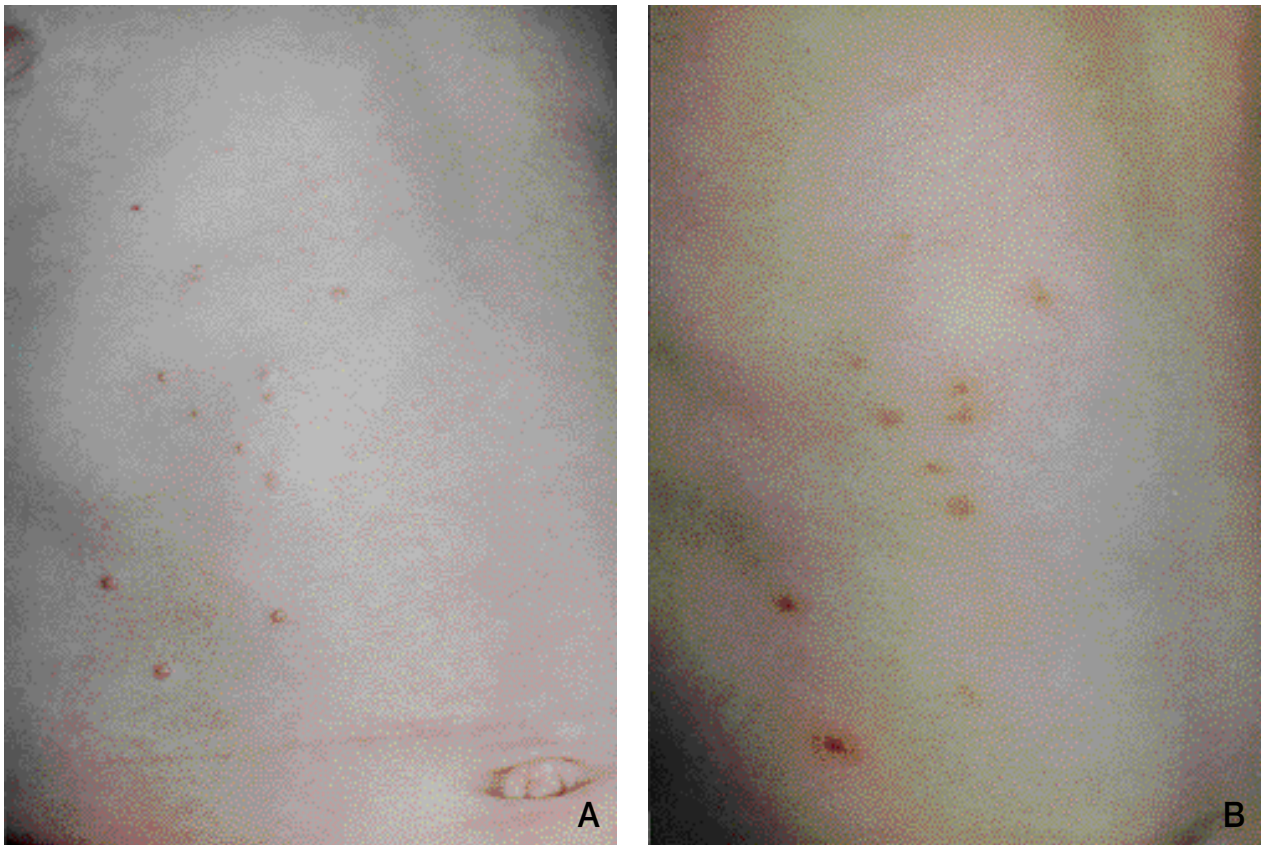

Figure 1. Molluscum contagiosum lesions on the trunk of patient at baseline (A) and after 12 weeks (B) of imiquimod therapy. Note the mild erythema surrounding each former molluscum papule.

(Table 3). This difference began at week 4 and continued until the end of the study.

Although the sampling unit in this study is the individual patient, the change in total number of MC lesions in patients also was assessed (Table 4). By week 12, the total number of lesions in all patients treated with imiquimod was reduced by 44.1%. In contrast, the number of lesions in all patients treated with vehicle increased by 5% by week 12.

Safety—Overall, imiquimod was well tolerated. Maximum severity scores in local skin reactions as graded by physicians or patients did not differ significantly between the imiquimod-treated group and the vehicle-treated group. Physician-assessed reactions included tenderness (P=.85, Wilcoxon rank sum test), erythema (P=.21), scaling (P=.214), excoriations (P=.08), and induration (P=.37). A higher percentage of patients in the imiquimod group, however, had erythema graded as moderate by the physician (58.3%) compared with patients in the vehicle group (22.2%). Whereas 33% of imiquimod patients had excoriation graded as mild by the physician, it was not noted in vehicle patients.

The distribution of maximum severity scores for pruritus as reported by the patient was also very similar in both treatment groups. A total of 6 (50%) and 5 (45.5%) patients in the imiquimod and vehicle groups, respectively, reported mild to moderate pruritus. Although pruritus may have been caused by imiquimod application, it is also a common symptom of MC. Similar rates of pruritus in both imiquimod and vehicle groups suggest that imiquimod treatment did not worsen the pruritus often seen with an MC infection. One patient each in both imiquimod and vehicle groups (8.3% and 9.1%, respectively) reported moderate pain and tenderness during the 12-week period. Overall, the incidence of the most intense patient-assessed local skin reactions was no different between imiquimod-treated skin and vehicle-treated skin and included pruritus (P=.816), pain (P=.962), tenderness (P=.48), and dryness (P=.44). To show how the severity of specific local skin reactions in the treatment area changed over the course of the

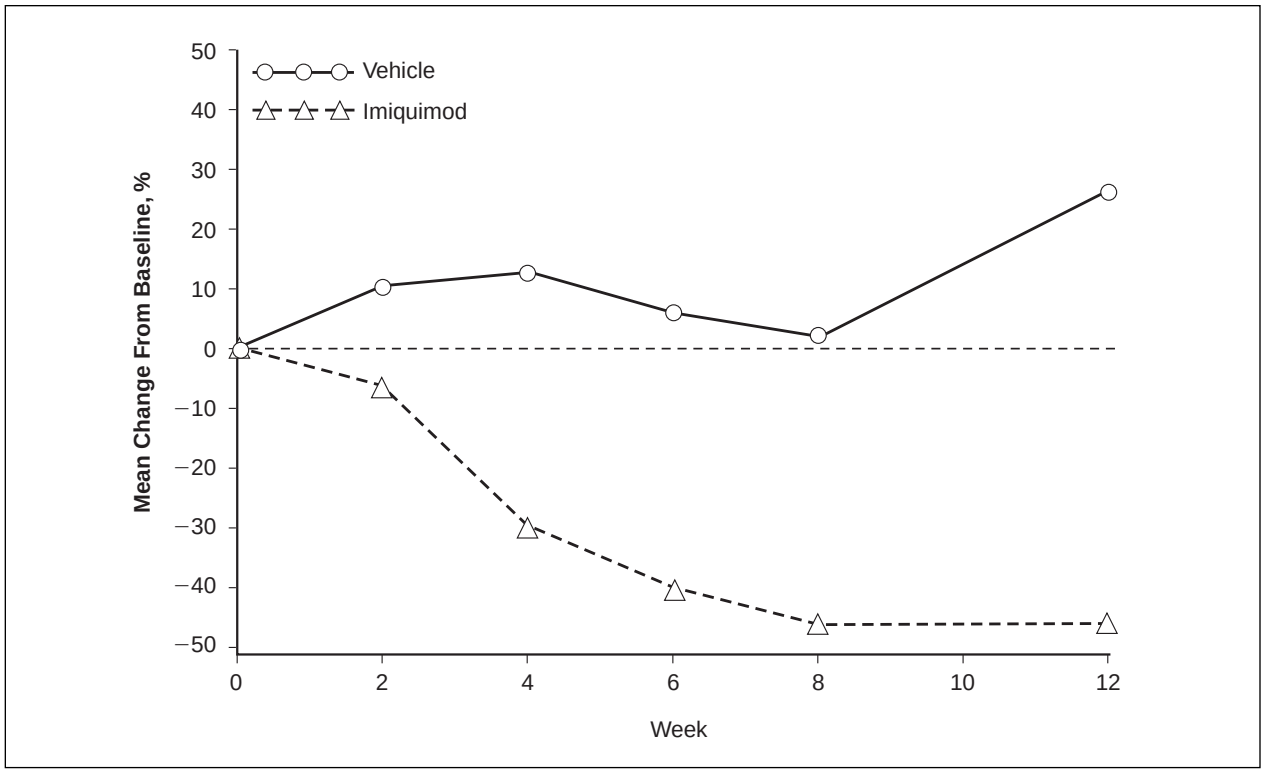

Figure 2. Mean percentage change in the number of molluscum contagiosum lesions from baseline by study week. A negative percentage indicates a decrease in the number of lesions.

Table 3.

Mean Number of Molluscum Contagiosum Lesions Cleared per Patient During the Study

	Imiquimod		Vehicle		
Study Week	No. of Patients*	Mean No. of Lesions Cleared	No. of Patients*	Mean No. of Lesions Cleared†	*P* Value‡
2	12	4.1	8	−1.8	.17
4	12	8.7	9	−1.8	.02
6	11	9.5	7	−0.9	.04
8	12	12.2	8	−0.8	.04
12	12	11.9	9	−0.9	.05
Treatment end point	12	11.9	11§	−0.7	.03

*Number of patients with an MC count at given week.
†A negative sign indicates an increase in lesion number.
‡Based on a 2-sided *t* test.
§In the treatment end-point analysis, patients missing a lesion count postbaseline assessment (n=2) were counted as having 0 lesions cleared.

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Table 4.

Clearance of Individual Molluscum Contagiosum Lesions From Baseline to End of Study

Treatment Group	n*	Study Visit	Total No. of Lesions	Total No. of Lesions Cleared From Baseline†	Lesions Cleared, %†
Imiquimod	12	Baseline	324		
		Week 12	181	143	44.1
Vehicle	9	Baseline	159		
		Week 12	167	−8	−5.0

*Number of patients with lesions counted at baseline and at study week 12.
†A negative number indicates an increase in lesions from baseline.

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treatment period, severity of physician-assessed local skin reaction also was analyzed at each clinic visit. No significant trends were noted.

Comment

Imiquimod cream 5% has been approved for the treatment of external genital warts since 1997 and is approved for use in children as young as 12 years. Imiquimod works by stimulating both the innate and cell-mediated immune responses against abnormal cells, including virally infected and neoplastic cells.[18] Based on this novel mechanism, imiquimod has been used in other dermatologic conditions, such as common warts and MC.[17,19,20] Imiquimod does not seem to have any age-specific safety concerns; however, large studies in children have yet to be conducted.

As with other poxviruses, the MCV codes for proteins that inhibit apoptosis of infected keratinocytes and antagonize the effects of cytokines.[21,22] T-helper lymphocyte responses are thought to be required to clear infection; the deficiency of lymphocyte responses in patients immunocompromised by human immunodeficiency virus infection contributes to the persistence and severity of MC in these patients and is consistent with the observed improvement with antiretroviral therapy.[23-25] Enhancement of the cell-mediated immune response by imiquimod, thus, represents a reasonable rationale for potential efficacy.

In this study, imiquimod was more effective than vehicle for clearing MC lesions. A 44.1% reduction in total lesions was observed in the imiquimod group, whereas the total number of lesions increased by 5% in the vehicle group. This clinically meaningful result is reflected in the statistically significant difference in the partial clearance rate between the 2 treatment groups (66.7% vs 18.2%, respectively). The complete clearance rate between the 2 treatment groups, however, was not statistically significant. This finding may be due in part to the higher mean number of lesions in imiquimod-treated patients, as well as the low number of patients in each treatment group. Based on the reported complete clearance rates for imiquimod and vehicle and the sample size used in this study, the power of this study was found to be 0.28. Thus, with the sample size used in this study, there was only a 28% chance of detecting a significant difference between imiquimod and vehicle in complete clearance rates.

The safety of imiquimod was evaluated by assessing the application site for erythema, pruritus, pain, tenderness, induration, excoriation, scaling, and dryness. These signs and symptoms also are associated with MC infection, presumably because the mechanism for spontaneous clearance is most likely an immune one. However, with a dose regimen of 3 times a week for 12 weeks, imiquimod treatment appeared to be well tolerated. While this observation was consistent with previously published anecdotes and studies,[14,15,18] this pilot study was the first to compare the active compound with a vehicle.

Although MC is a self-limiting condition,[26,27] treatment is warranted in patients who experience discomfort, autoinoculate themselves, infect siblings

or classmates, or present with extensive disease. Many younger patients do not tolerate painful, physical ablative treatments, such as curettage or cryotherapy. Chemical ablation with cantharidin is very useful when patients present with a few lesions; however, discomfort after the MC lesions blister can be limiting in patients with many lesions.[9] In addition, the potential risk for blistering at sensitive areas, such as the face and groin, further justifies the use of topical imiquimod. Imiquimod cream offers an alternative to both chemical and physical ablative therapies. Although not approved for MC or in patients younger than 12 years, imiquimod was well tolerated and effective in this small study. Larger, double-blind randomized studies are warranted to confirm the findings of this pilot study.

REFERENCES

1. Gottlieb SL, Myskowski PL. Molluscum contagiosum. *Int J Dermatol.* 1994;33:453-461.
2. Cribier B, Scriverner Y, Grosshans E. Molluscum contagiosum: histologic patterns and associated lesions. a study of 578 cases. *Am J Dermatol.* 2001;23:99-103.
3. Hawley TG. The natural history of molluscum contagiosum in Fijian children. *J Hyg (Lond).* 1970;68:631-632.
4. Overfield TM, Brody JA. An epidemiologic study of molluscum contagiosum in Anchorage, Alaska. *J Pediatr.* 1966;69:640-642.
5. Janniger CK, Schwartz RA. Molluscum contagiosum in children. *Pediatr Dermatol.* 1993;52:194-196.
6. Syed TA, Lundin S, Ahmad M. Topical 0.3% and 0.5% podophyllotoxin cream for self-treatment of molluscum contagiosum in males. a placebo-controlled, double-blind study. *Dermatology.* 1994;189:65-68.
7. Romiti R, Ribeiro AP, Grinblat BM, et al. Treatment of molluscum contagiosum with potassium hydroxide: a clinical approach in 35 children. *Pediatr Dermatol.* 1999;16:228-231.
8. Rönnerfält L, Fransson J, Wahlgren CF. EMLA cream provides rapid pain relief for the curettage of molluscum contagiosum in children with atopic dermatitis without causing serious application-site reactions. *Pediatr Dermatol.* 1998;15:309-312.
9. Silverberg NB, Sidbury R, Mancini AJ. Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients. *J Am Acad Dermatol.* 2000;43:503-507.
10. Niizeki K, Hashimoto K. Treatment of molluscum contagiosum with silver nitrate paste. *Pediatr Dermatol.* 1999;16:395-397.
11. Valentine CL, Diven D. Treatment modalities for molluscum contagiosum. *Dermatol Ther.* 2000;13:285-289.
12. Cunningham BB, Paller AS. Inefficacy of oral cimetidine for nonatopic children with molluscum contagiosum. *Pediatr Dermatol.* 1998;15:71-72.
13. Imbertson LM, Beaurline JM, Couture AM, et al. Cytokine induction in hairless mouse and rat skin after topical application of the immune response modifiers imiquimod and S-28463. *J Invest Dermatol.* 1998;110:734-739.
14. Hengge UR, Esser S, Schultewolter T, et al. Self-administered topical 5% imiquimod for the treatment of common warts and molluscum contagiosum. *Br J Dermatol.* 2000;143:1026-1031.
15. Liota E, Smith KJ, Buckley R, et al. Imiquimod therapy for molluscum contagiosum. *J Cutan Med Surg.* 2000;4:76-82.
16. Barba AR, Kapoor S, Berman B. An open label safety study of topical imiquimod 5% cream in the treatment of molluscum contagiosum in children [clinical trial]. *Dermatol Online J.* 2001;7:20.
17. Skinner RB Jr, Ray S, Talanin NY. Treatment of molluscum contagiosum with topical 5% imiquimod cream [letter]. *Pediatr Dermatol.* 2000;17:420.
18. Testerman TL, Gerster JF, Imbertson LM, et al. Cytokine induction by the immunomodulators imiquimod and S-27609. *J Leukoc Biol.* 1995;58:365-372.
19. Moresi JM, Herbert CR, Cohen BA. Treatment of anogenital warts in children with topical 0.05% podofilox gel and 5% imiquimod cream. *Pediatr Dermatol.* 2001;18:448-452.
20. Grussendorf-Conen EI, Jacobs S. Efficacy of imiquimod 5% cream in the treatment of recalcitrant warts in children. *Pediatr Dermatol.* 2002;19:263-266.
21. Shisler JL, Moss B. Molluscum contagiosum virus inhibitors of apoptosis: the MC159 v-FLIP protein blocks Fas-induced activation of procaspases and degradation of the related MC160 protein. *Virology.* 2001;282:14-25.
22. Xiang Y, Moss B. IL-18 binding and inhibition of interferon gamma induction by human poxvirus-encoded proteins. *Proc Natl Acad Sci U S A.* 1999;96:11537-11542.
23. Schwartz JJ, Myskowski PL. Molluscum contagiosum in patients with human immunodeficiency virus infection. *J Am Acad Dermatol.* 1992;27:583-588.
24. Calista D, Boschini A, Landi G. Resolution of disseminated molluscum contagiosum with highly active anti-retroviral therapy (HAART) in patients with AIDS. *Eur J Dermatol.* 1999;9:211-213.
25. Matis WL, Triana A, Shapiro R, et al. Dermatologic findings associated with human immunodeficiency virus infection. *J Am Acad Dermatol.* 1987;17(suppl 5, pt 1):746-751.
26. National guideline for the management of molluscum contagiosum. Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). *Sex Transm Infect.* 1999;75(suppl 1):S80-S81.
27. Weston WL, Lane AT. Should molluscum be treated [letter]? *Pediatrics.* 1980;65:865.