PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Imiquimod, Molluscum, and the Need for a Better "Best Pharmaceuticals for Children" Act

Kenneth A. Katz and Glenda L. Swetman

Pediatrics; originally published online June 24, 2013;
DOI: 10.1542/peds.2013-0116

PEDIATRICS PERSPECTIVES

Imiquimod, Molluscum, and the Need for a Better "Best Pharmaceuticals for Children" Act

AUTHORS: Kenneth A. Katz, MD, MSc, MSCE, and Glenda L. Swetman, MD

The Permanente Medical Group, Inc., Pleasanton, California

KEY WORDS
molluscum contagiosum, imiquimod, clinical trials, public policy

ABBREVIATIONS
BPCA—Best Pharmaceuticals for Children Act
FDA—Food and Drug Administration
MC—Molluscum contagiosum
PI—package insert
RCT—randomized controlled trial

Dr Katz conceptualized the manuscript and drafted the initial manuscript; Dr Swetman helped conceptualize the manuscript and reviewed and revised the manuscript; and both authors approved the final manuscript as submitted.

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of The Permanente Medical Group, Inc.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-0116

doi:10.1542/peds.2013-0116

Accepted for publication Apr 17, 2013

Address correspondence to Kenneth A. Katz, MD, MSc, MSCE, The Permanente Medical Group, Inc., 7601 Stoneridge Dr, Second Floor, Pleasanton, CA 94588. E-mail: kenneth.katz@gmail.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *Dr Katz is a contributor to several of the publications listed in Supplemental Table 1, including* VisualDx, Decision Support in Medicine, *and* Fitzpatrick's Dermatology in General Medicine. *He is a shareholder in Synta Pharmaceuticals Corp. Dr Swetman has indicated she has no financial relationships relevant to this article to disclose.*

FUNDING: No external funding.

It was the best research Emily's doctor had never heard about.*

Emily was a delightful 6-year-old with molluscum contagiosum (MC). Characteristic dome-shaped umbilicated papules, some of them itchy, peppered her chest and buttocks. Emily had returned to the clinic, where one of us (KAK) saw her, after she failed treatment with imiquimod 5% cream.

Coincidentally, Emily was born just as 2 rigorously conducted randomized controlled trials (RCTs) of imiquimod for treatment of MC in children were concluding. In both studies, imiquimod proved ineffective. Six years later, and 5 years after imiquimod's package insert (PI) had been updated to include those RCT results, no studies had shown otherwise.

So why was Emily prescribed imiquimod? It would be easy to blame Emily's doctor.

But it's not that simple.

The real problem lies in a federal law that allows data from pediatric drug studies requested by the federal government and subsidized by taxpayers to escape meaningful dissemination to physicians. As a result, children like Emily are needlessly exposed to ineffective and/or unsafe medicines.

Imiquimod was first approved by the Food and Drug Administration (FDA) for treatment of genital warts in adults in 1997. Physicians soon began using it off-label to treat MC in children.

There were good reasons for that. First, other treatments were inconvenient and/or poorly tolerated. Second, imiquimod had proven effective for genital warts, which like MC are caused by a virus. Third, numerous observational studies and review articles, as well as 2 small RCTs, suggested that imiquimod might work.

But the evidence was not overwhelming, and imiquimod is not benign. It can cause application site reactions and, rarely, flulike symptoms and other systemic adverse effects.

To address questions about imiquimod's safety and efficacy in treating MC in children, the FDA stepped in, using its authority under the Best Pharmaceuticals in Children Act (BPCA). Signed into law in 2002 and

*The name of the child discussed in the manuscript has been changed to protect her privacy.

made permanent in 2012, BPCA is a major pillar of the federal government's efforts to promote pediatric drug research.

The need for more research stems from the existence of potentially dangerous gaps in knowledge about prescription drug use in children. Although children often respond to drugs differently from adults, drug companies often lack financial incentives to study drugs in children.[1]

The BPCA enables the FDA to offer drug companies a quid pro quo. The FDA gets data from specifically requested pediatric studies of drugs used for conditions deemed of public health importance. In return, FDA rewards companies with 6-month marketing exclusivity extensions for a drug, worth up to $500 million.[2]

The BPCA has spurred substantial pediatric drug research and rewards: >300 study requests, >44 000 children enrolled in studies, >100 PI amendments, and >100 marketing exclusivity extensions granted.[1]

Regarding imiquimod, FDA requested 2 RCTs and 1 pharmacokinetic study, all in children aged 2 to 12 years with MC.[3] In 2006, 3M, imiquimod's original manufacturer, received a marketing exclusivity extension after having completed the RCTs and the pharmacokinetic study, which enrolled 702 and 22 children, respectively.[3]

The study results were clear: imiquimod did not work. In both studies, a similar proportion (~25%) of both imiquimod- and vehicle-treated children cleared their MC after 18 weeks.[3,4]

However, imiquimod might harm children. In the RCTs more imiquimod-treated children experienced application-site reactions (by far the most commonly reported adverse effect of imiquimod, in both children and adults) as well as otitis media, conjunctivitis, leukopenia, and lymphadenopathy.[3,4]

In the pharmacokinetic study, in which imiquimod was applied to at least 10% of body surface area ("maximal use conditions"), systemic absorption was detected after just 1 dose.[3–5] White blood cell (WBC) and absolute neutrophil counts decreased; 40% and 25% of subjects, respectively, experienced leukopenia or neutropenia.[3] "These findings," the FDA reviewer wrote, "may be due to systemic effects of imiquimod."[3]

As a result, imiquimod's PI was amended in 2007 to state that "efficacy was not demonstrated for MC in children aged 2–12" and to present additional pharmacokinetic and safety information, including effects on white blood cell and absolute neutrophil counts.[4] In accordance with BPCA requirements, the FDA posted its review of the studies on its Web site.[3]

For its part, 3M and its coinvestigators published the pharmacokinetic study in a peer-reviewed, PubMed-indexed journal, proving a more favorable interpretation of the results than that in the FDA review or the PI amendment. The drug's effects on blood counts, the authors wrote, were "not considered to be clinically meaningful," and percutaneous absorption was judged "minimal or very low."[5] In passing, in the second-to-last paragraph of the discussion section, the article mentioned the 2 RCTs and also, interestingly, hypothesized that characteristics of the MC virus genome could explain imiquimod's lack of efficacy.[5] 3M also posted summaries of all 3 studies on a now-defunct industry-sponsored Web site.

3M never published the RCTs themselves in a journal. The BPCA does not require companies to do so.

Not that they would have been difficult to publish. Many journals likely would have been interested in publishing the RCTs. MC is a common condition and therefore of substantial interest to clinicians. The RCTs upended conventional thinking about imiquimod's effectiveness while raising pediatric safety concerns.

However, failure to have published the RCTs in a peer-reviewed, PubMed-indexed journal means, practically, that doctors like Emily's are unlikely to know about them. Practicing physicians generally do not peruse PIs for updates, scour pharmacokinetic study reports, or search the FDA Web site for BPCA-related reviews. Rather, when looking to the medical literature to solve clinical problems, physicians might search for clinical trials on PubMed or, more likely, for review articles in medical journals, textbook chapters, or online reference guides.

Yet no major dermatology or pediatrics textbooks or online references, all published since 2007, even mention the 2 negative imiquimod RCTs (Supplemental Table 1). Nor does an exhaustively researched Cochrane Collaboration systematic review on MC, updated in 2009 (Supplemental Table 1). Nearly all include imiquimod as a reasonable treatment option. (The sole exception is a dermatology textbook that recommends against imiquimod on the basis of an alleged lack of trial data.)

Moreover, RCTs of imiquimod for MC in children continue to be designed, conducted, and reported without reference to the 2 BPCA RCTs.[6]

This is not the first time that publication of studies conducted under BPCA or similar programs has been found lacking. One study found that only 44% of such studies were published in an indexed, peer-reviewed journal.[7] Emily's experience illustrates the continuing hazard to evidence-based practice posed by lack of publication of BPCA studies.

It's time to fix the problem.

Congress should amend BPCA by requiring publication of studies in peer-reviewed medical journals as an additional condition for marketing exclusivity extensions, as others have advocated.[7] Acceptable journals should

include only those indexed by the government-sponsored, freely available PubMed database.

For their part, authors of textbook chapters and other reviews should be more diligent in reviewing PIs and the FDA Web site. Physicians should also periodically review PIs for updates.

In the specific case of imiquimod and MC, the investigators of the 2 negative RCTs should publish the studies in a peer-reviewed, PubMed-indexed journal; textbooks and other reviews should be updated to include the studies; researchers should reference the 2 negative RCTs in conducting (or not conducting) additional RCTs; and, crucially, physicians should cease prescribing imiquimod to treat MC in children.

Problems related to incomplete publication of RCT results and deficiencies in evidence-based practice are not, of course, limited to BPCA studies. Failure to remedy all of those problems, however, should not preclude remedying the law meant to lead to the best health care possible for children like Emily.

ACKNOWLEDGMENT

We thank Amy E. Karon, DVM, MPH, for helpful comments in preparing this manuscript.

REFERENCES

1. Institute of Medicine. 2008. *Addressing the Barriers to Pediatric Drug Development: Workshop Summary.* Washington, DC: The National Academies Press. Available at: http://www.iom.edu/Reports/2008/Addressing-the-Barriers-to-Pediatric-Drug-Development-Workshop-Summary.aspx. Accessed April 29, 2013
2. Li JS, Eisenstein EL, Grabowski HG, et al. Economic return of clinical trials performed under the pediatric exclusivity program. *JAMA.* 2007;297(5):480–488
3. Papadopoulos EJ. *Clinical Executive Summary* [Imiquimod]. Available at: www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM162961.pdf. Accessed December 6, 2012
4. Aldara (imiquimod) cream for topical use. Prescribing information, revised 4/2007. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=7fccca4e-fb8f-42b8-9555-8f78a5804ed3. Accessed January 12, 2013
5. Myhre PE, Levy ML, Eichenfield LF, Kolb VB, Fielder SL, Meng TC. Pharmacokinetics and safety of imiquimod 5% cream in the treatment of molluscum contagiosum in children. *Pediatr Dermatol.* 2008;25(1):88–95
6. Al-Mutairi N, Al-Doukhi A, Al-Farag S, Al-Haddad A. Comparative study on the efficacy, safety, and acceptability of imiquimod 5% cream versus cryotherapy for molluscum contagiosum in children. *Pediatr Dermatol.* 2010;27(4):388–394
7. Benjamin DK, Jr, Smith PB, Murphy MD, et al. Peer-reviewed publication of clinical trials completed for pediatric exclusivity. *JAMA.* 2006;296(10):1266–1273

Imiquimod, Molluscum, and the Need for a Better "Best Pharmaceuticals for Children" Act

Kenneth A. Katz and Glenda L. Swetman

Pediatrics; originally published online June 24, 2013;
DOI: 10.1542/peds.2013-0116

Supplemental Information

SUPPLEMENTAL TABLE 1 Use of Imiquimod to Treat Molluscum Contagiosum (MC), According to Major Dermatology, Pediatric Dermatology, and Pediatrics Textbooks, Online References, and Review Articles

Reference Name	Year of Publication	Mentions 1 Large RCTs?	Comments on Use of Imiquimod to Treat MC
Dermatology textbooks			
Andrews' Diseases of the Skin: Clinical Dermatology	2011	No	"No controlled trials have confirmed the efficacy of imiquimod and it cannot be recommended for the treatment of molluscum."[1]
Clinical Dermatology	2010	No	"Nightly application of the immunomodulatory drug imiquimod (Aldara cream) has been reported to be effective in both immunocompromised and immunocompetent children and adults."[2]
Dermatology	2008	No	Imiquimod is listed in table of treatments for MC, under highest category (1) of evidence-based support ("prospective controlled trial").[3]
Fitzpatrick's Dermatology in General Medicine	2012	No	Imiquimod listed in table of treatments for MC, under highest category (1) of evidence-based support ("double-blind studies").[4]
Pediatric dermatology textbooks			
Harper's Textbook of Pediatric Dermatology	2011	No	"In six studies, including two double-blind controlled trials, imiquimod was successful in completely or partially clearing MC in immunocompetent patients, including children."[5]
Hurwitz Clinical Pediatric Dermatology	2011	No	"Imiquimod cream has been used with different treatment regimens, from three times weekly to application on a daily basis, with variable results."[6]
Pediatric Dermatology	2011	No	"There has been some success reported with the use of imiquimod 1-5% cream, but in some cases the irritation caused led to a spread of new lesions."[7]
Pediatrics textbooks			
Rudolph's Pediatrics	2011	No	Imiquimod listed as a treatment of MC.[8]
Nelson Textbook of Pediatrics	2011	No	"Imiquimod applied topically is beneficial if not excessively irritating."[9]
Pediatric infectious diseases textbook Principles and Practice of Pediatric Infectious Diseases	2012	No	"Several topical treatments are available, including imiquimod, tretinoin, and cantharidin."[10]
Systematic review			
Cochrane collaboration	2009	No	Includes small published RCT ($N = 23$) of imiquimod for MC; states that differences between imiquimod and placebo group were not statistically significant.[11]
Online references			
Decision Support in Medicine	2012	No	Imiquimod "is used off-label for treatment of MCV [MC virus]. Erythema and irritation are the most common side effects, but may also be a sign of efficacy."[12]
DynaMed	2012	No	Imiquimod listed as "topical treatment with limited evidence of benefit"; "imiquimod 1% cream 3 times daily 5 days/week may be highly effective in older children and adults (level 2 [mid-level] evidence); "imiquimod 5% cream 5 days/week may be as effective as cryotherapy in children with MC (level 2 [mid-level] evidence)"; "imiquimod 3 times/week partially effective in children in pilot study (level 2 [mid-level] evidence)"[13]
Medscape	2012	No	"An immune response modifier approved for the treatment of external genital and perianal warts in adults, imiquimod cream has been reported to be effective in the treatment of MC; imiquimod cream may be used in conjunction with cantharidin."[14]
UpToDate	2012	No	Imiquimod listed as a second-line therapy for MC.[15]
VisualDx	2012	No	"Although it is not FDA-approved for treatment of MC, imiquimod 5% cream is well tolerated in children and has been shown to be efficacious."[16]

REFERENCES

1. James WD, Berger TG, Elston DM. *Andrews' Diseases of the Skin: Clinical Dermatology.* 11th ed. London, England: Saunders Elsevier; 2011:389
2. Habif TP. *Clinical Dermatology.* 5th ed. Edinburgh, Scotland: Mosby, 2010:466
3. Mancini AJ, Shani-Adir A. Other viral diseases. In: Bolognia JL, Jorizzo JL, Rapini RP, eds. *Dermatology.* 3rd ed. Philadelphia: Elsevier Saunders, 2012:1359
4. Piggott C, Friedlander SF, Tom W. Poxvirus infections. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller A, Leffell D, Wolff K, eds. *Fitzpatrick's Dermatology in General Medicine.* 8th ed. Available at: http://accessmedicine.com/content.aspx?aID=56089246. Accessed May 17, 2013
5. Alikhan A, Shwayder T. Molluscum contagiosum. In: Irvine AD, Hoeger PH, Yan AC, eds. *Harper's Textbook of Pediatric Dermatology.* 3rd ed. Hoboken, NJ: Wiley-Blackwell; 2011:46.5
6. Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology.* 4th ed. Edinburgh, Scotland: Elsevier Saunders; 2011:365
7. Mancini AJ, Wargon O. Viral infections. In: Schachner LA, Hansen RC, eds. *Pediatric Dermatology.* 4th ed. Mosby: 2001. p. 1468
8. Dohil MA, Eichenfield LF. Molluscum Contagiosum. In: Rudolph's Pediatrics, 22nd ed. Ed: Rudolph CD. New York: McGraw Hill Medical, 2011. Accessed in www.AccessPediatrics.com, December 11, 2012
9. Morelli JG. Cutaneous Viral Infections. In: Nelson Textbook of Pediatrics, 19th ed. Ed: Kliegman RM, Stanton BF, Schor NF, et al. Philadelphia: Elsevier/Saunders, 2011. p. 2317
10. Moore ZS. Poxviridae. In: Principles and Practice of Pediatric Infectious Diseases, 4th ed. Ed: Long SS. Edinburgh, Scotland: Elsevier Saunders, 2012. p. 1025
11. van der Wouden JC, van der Sande R, van Suijlekom-Smit LW, et al. Interventions for cutaneous molluscum contagiosum. Cochrane Database Syst Rev. 2009;4:CD004767
12. Levy ML, Gordon J. Molluscum Contagiosum (Molluscipoxvirus). In: Decision Support in Medicine [online reference]. https://www.decisionsupportinmedicine.com/DSM/a/articles/2/M/1216. Accessed December 11, 2012
13. Molluscum contagiosum. In: DynaMed [online reference]. Ed: Alper BS. Available at: http://web.ebscohost.com/dynamed/detail?vid=3&hid=123&sid=f8471e1f-8cc4-41b7-b1d6-eca9ca055420%40sessionmgr104&bdata=JnNpdGU9ZHIuYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=116448. Accessed November 13, 2011
14. Bhatia AC. Molluscum Contagiosum. In: Medscape [online reference], ed. Elston DM. Available at: http://emedicine.medscape.com/article/910570-treatment#aw2aab6b6b2. Updated January 5, 2012. Accessed December 11, 2012
15. Isaacs SN. Molluscum contagiosum. UpToDate [online reference]. Available at www.UpToDate.com/contents/molluscumcontagiosum?view=print. Accessed November 13, 2011
16. Stein S, Wiss K, Galbraith S, et al. Molluscum Contagiosum. In: VisualDx.com[online reference]. Available at: http://www.visualdx.com/visualdx/visualdx6/getDiagnosisText.do?moduleId=10&diagnosisId=53976. Updated May 22, 2012. Accessed December 11, 2012