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

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.5

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.”5

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.”3 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 remedi- ing the law meant to lead to the best health care possible for children like Emily.

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REFERENCES
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