Unethical use of imiquimod as a comparator group in a randomized clinical trial of children with molluscum contagiosum

To the Editor: Conducting ethical clinical research requires minimizing risks to research participants.[1] A randomized controlled trial (RCT) comparing ingenol mebutate 0.015% gel with imiquimod 5% cream in children[2] failed to meet that standard.

In that RCT, children randomized to the imiquimod group were exposed to a medicine that is no more effective than vehicle in treating molluscum contagiosum, as previously shown in 2 rigorously conducted, vehicle-controlled RCTs that enrolled 323 and 379 children, respectively.[3] But imiquimod should not be "considered a placebo arm" in the ingenol-imiquimod RCT, as the investigators wrote.[2] Imiquimod is not inactive and has known potential harms for children.

In the 2 large imiquimod—molluscum contagiosum RCTs, a related pharmacokinetic study, and a related phase 2 study—all conducted by imiquimod's then-manufacturer at the request of the Food and Drug Administration—imiquimod-treated children were more likely than vehicle-treated children to experience important adverse events, including application-site reactions, otitis media, conjunctivitis, abnormal blood cell counts, and lymphadenopathy.[3] In 2007, reflecting those findings, Food and Drug Administration—approved prescribing information for imiquimod was updated to explicitly note imiquimod's lack of demonstrated effectiveness in treating molluscum contagiosum and its potential harms to children.[4] The 2 large imiquimod—molluscum contagiosum RCTs have never been published in the medical literature. However, numerous articles since 2013 have used publicly available Food and Drug Administration analyses to highlight results of the RCTs and caution against using imiquimod to treat children with molluscum contagiosum.[5]

It should not be surprising that imiquimod-treated children in the ingenol-imiquimod RCT experienced adverse events, including pain, pruritus, and "crusts on the molluscum contagiosum lesions."[2] Those imiquimod-related harms were unnecessary. The RCT should have used ingenol vehicle rather than imiquimod as a comparison arm. Using ingenol vehicle would have eliminated imiquimod-related risks to participants while enabling the RCT to investigate ingenol's effectiveness and safety in children with molluscum contagiosum. Vehicle-controlled RCTs for ingenol, in fact, were used to support its sole Food and Drug Administration approval, in 2012, for treatment of actinic keratosis.

Because of imiquimod's ineffectiveness and potential harms when used to treat molluscum contagiosum in children, studies that expose children with molluscum contagiosum to imiquimod should not, in the absence of compelling new evidence, be designed or conducted by investigators, approved by institutional review boards, or published by medical journals.

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