

Assessing risk: Data from montelukast clinical trials

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The US Food and Drug Administration (FDA)'s most recent updated information on leukotriene inhibitors dated August 28, 2009, states that postmarket cases of neuropsychiatric events have been reported for the leukotriene inhibitors montelukast, zafirlukast, and zileuton.¹ Cases included agitation, aggression, anxiousness, dream abnormalities, hallucination, depression, insomnia, irritability, restlessness, suicidal thinking and behavior, and tremor. The FDA recommends that patients should be informed of the potential for these events.

Many patients will request additional information, and providers will seek to quantify the risk for their patients. This issue of the *Journal* contains 2 articles that inform further estimation of these risks. Both articles examined adverse events from Merck-sponsored clinical trials of montelukast. Philip et al² investigated possible suicidal adverse events that occurred during clinical trials, and in a separate report Philip et al³ examined behavior-related adverse events. As reported in the conflict of interest section, employees of Merck and Co, Inc, authored both articles.

The articles were the result of scientific reviews requested by and in part specified by the FDA. In the article reporting suicidality in montelukast clinical trials,² the authors used 2 methods. The first descriptive review encompassed all adverse events related to suicidality from trials regardless of age and indication and included open-label, active-control, and placebo-control trials. Although the inclusion of this broad range of trials limits statistical comparisons, the strength is that the reader can review all possible suicide-related adverse events. In the second analysis² the authors used methodology that was initially developed to examine possible suicide-related adverse events during clinical trials of antidepressants by a group with expertise in suicidality.⁴ The montelukast trials included in the second approach were all placebo controlled, with age limitation of 6 years or older. The strength of this method was the adjudication of all possible suicide-related adverse events by the Suicide Classification Center at Columbia University in New York blinded to treatment group. In addition to weaknesses outlined by the authors, a further potential weakness is the initial transcription of the adverse events by Merck employees. Despite this limitation, the results of both methods suggest that the risk of suicidal ideation is low. In method

2, 1 patient per 22,433-montelukast treated patients was classified with suicidal ideation versus none of the 7,780 patients in the placebo group and none of the 4,724 patients in the control group.

The analysis of behavior-related adverse events in montelukast clinical trials uses methodology that readers might be unfamiliar with, the controlled vocabulary Medical Dictionary for Regulatory Activities. This method enables investigators to map adverse events onto a hierarchy of specified terms and categories. Although the FDA approved the groupings and prespecified analyses, some of the groupings for analysis were not intuitive. The prespecified analyses show no significant difference between placebo- and montelukast-treated patients with respect to behavior-related adverse events; the frequency of events appeared to be low at 2.73%. Serious behavior-related events occurred at 0.03% in 11,673 patients who received montelukast and was similar to the frequency seen in 8,827 patients in placebo groups. Of interest, analyses within the age groups of 12 to 17 years and subjects older than 65 years revealed that patients treated with montelukast were at higher risk than patients who received placebo.

Individuals with serious mental health disorders might be at highest risk for suicidality and behavior-related adverse events, yet this risk is hard to estimate because they are often excluded from clinical trials. Unfortunately, this group might be at risk for more severe asthma because both adults and children with more severe asthma are at increased risk for depression and behavior-related problems.^{5,6} Health care providers of individuals with asthma and atopic disorders should screen for mental health symptoms⁷ and consider referral of patients with suspected mental illness. In addition, health care providers should not assume the behavioral risk of leukotriene inhibitors outweighs the benefit to asthma. Rather, as with all patients, the provider should inform these patients of estimates of both risks and benefits. Helping patients make informed decisions may involve working with the patient's mental health provider. This can be facilitated by establishing relationships with mental health providers who have expertise in working with patients comorbid for asthma or other atopic illnesses.

Both articles^{2,3} comment that the studies were not originally designed to assess suicidality or behavior-related adverse events. In the future, the FDA might consider mandating standardized methodology to assess these adverse events as new medicines are developed and tested.

The 2 articles^{2,3} described above were initiated after the post-marketing reporting of adverse events. The authors comment that given the higher rate of psychiatric comorbidity in individuals with asthma and atopy, it is not surprising that postmarket events possibly related to psychiatric illnesses have been reported. However, there might be an additional factor contributing to increased postmarket reporting, and this is a lack of trust from the public in both the pharmaceutical industry and the government body that oversees it. As initial reports are publicized, the chance of subsequent reports might increase. Many processes are currently underway to recapture the public's trust, including

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increasing the transparency of the FDA and the pharmaceutical industry and relationships between pharmaceutical firms, health care providers, and the government. The health care provider who is informed regarding both risks and benefits to patients will also be instrumental in helping to reinforce the public's trust of the medical system.

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