Data Sought on Motavizumab Hypersensitivity

BY ELIZABETH MECHCATIE

FROM A MEETING OF THE FDA'S ANTIVIRAL DRUG PRODUCTS ADVISORY COMMITTEE

SILVER SPRING, MD. — More information on the risks and severity of hypersensitivity reactions associated with the monoclonal antibody motavizumab is needed before it is approved for preventing serious lower respiratory tract infections with respiratory syncytial virus in high-risk infants, according to the majority of a Food and Drug Administration advisory panel.

The FDA's Antiviral Drug Products Advisory Committee voted 14 to 3 against recommending approval of motavizumab for the indication proposed by its manufacturer, MedImmune LLC: the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk for RSV disease (premature infants, children with chronic lung disease of prematurity, and children with hemodynamically significant congenital heart disease).

Like palivizumab (Synagis), approved in 1998 for RSV prophylaxis, motavizumab is a monoclonal antibody that binds to the F protein of RSV, but has a higher binding affinity to the protein and exerts a greater degree of neutralizing activity against RSV isolates in vitro, according to MedImmune, which also manufactures palivizumab. The proposed dosing for motavizumab is the same as for palivizumab: 15 mg/kg, administered by intramuscular injection once a month during the RSV season. Several panelists voiced concerns that Medimmune would phase out palivizumab once motavizumab was approved; a MedImmune spokesperson said that the company has never made a statement about such plans.

Panelists agreed that motavizumab had been shown to be effective in preventing RSV, but although the data suggested that it might be more effective than palivizumab, they agreed that it had not been shown to be superior. Moreover, the potential for hypersensitivity reactions among those on motavizumab in clinical trials was a major safety concern that needed to be studied further before approval, including in children who were more severely ill than those in the clinical trials. Although these reactions were rare, they were significant when they occurred and appeared to have an immunologic basis, according to the panel.

"Hypersensitivity and skin issues aside, I'm not really seeing a difference," said panelist Patrick Clay, Pharm.D., director of the Dybedal Center for Clinical Research, Kansas City (Mo.) University. While it would be helpful to have more than one option for RSV prophylaxis, he pointed out that with the data available, it was unclear how a clinician would choose one or the other.

Panelist Dr. Yvonne Maldonado, chief of infectious diseases, Packard Children's Hospital, Stanford (Calif.) University, said that there was a "strong suggestion" that motavizumab was more effective than palivizumab, but there were not enough differences between the two drugs at this point to help practicing clinicians decide when the newer drug should be used. A "better definition of the safety profile would be really helpful for the clinician," she noted.

There is a 'strong suggestion' that motavizumab is more effective than palivizumab for RSV prophylaxis, but a better definition of the safety profile would be helpful for clinicians.

In a phase III randomized, double-blind noninferiority study, motavizumab was compared with palivizumab in 6,635 premature infants (under 35 weeks' gestation) who were younger than 6 months, and in children younger than 24 months who had been premature and had chronic lung disease, in a 1:1 ratio. (Both drugs were administered at a dosage of 15 mg/kg once a month for five doses.) The proportion of patients who were hospitalized for RSV, the primary end point, was 1.4% among those on motavizumab, compared with 1.9% of those on palivizumab, which met the noninferiority criteria for the study. (Most of the patients in each group completed the study and about 96% in each group received all five scheduled doses.)

The overall safety profiles were similar between the two groups, with the exception of hypersensitivity reactions: More patients who received motavizumab developed urticaria (0.4%) and allergic rash (0. 8%), compared with those on palivizumab (0.1% and 0.3%). In addition, eight of those on motavizumab had a grade 3-4 hypersensitivity reaction, compared with none of those on palivizumab.

In the five studies that comprised the entire safety database for motavizumab, there were 19 grade 3-4 hypersensitivity events among those on motavizumab, compared with none among those on palivizumab. Of the 5,360 patients who received motavizumab, there were three cases "suggestive of anaphylaxis," according to the FDA reviewer.

In a study that was considered a supportive study, motavizumab was compared with placebo in 1,410 Native American term infants, who were at a greater risk of RSV infections. The incidence of RSV hospitalizations was 8.3% among those on motavizumab compared with 1.4% among those on placebo, a significant difference.

The allergist on the panel, Dr. Prescott Atkinson, professor and director of the division of pediatric allergy and immunology, Children's Hospital, Birmingham, Ala., said he voted against approval because he was convinced that the risks were higher with this drug, but "it's not clear to me that it's more efficacious than the drug we already have."

If studies showed it was 10% more effective than palivizumab in reducing hospitalizations, then the risks of non–life-threatening skin reactions and rare cases of more severe anaphylaxis "might be acceptable risks in this high-risk population who comes in and not infrequently expires from RSV," he added.

Since approval, an estimated 1.2 million people have received palivizumab and 10 cases of anaphylaxis have been reported to the FDA's voluntary adverse event reporting program, according to the FDA.

A warning about the potential for anaphylaxis is on the palivizumab label.

If motavizumab is approved, MedImmune plans to market the drug as Rezield, with a risk management plan that would include educating prescribers about how to manage skin reactions.

The plan also would involve enhanced vigilance of adverse events. Postmarketing studies would address issues that include evaluating the rates and severity of hypersensitivity reactions associated with motavizumab, the emergence of motavizumab-resistant RSV, and adverse event rates in the real-world setting. ■

Palivizumab May Shorten Hospital Stay, Calif. Data Indicate

BY PATRICE WENDLING

FROM THE ANNUAL MEETING OF THE PEDIATRIC ACADEMIC SOCIETIES

VANCOUVER, B.C. — The introduction of palivizumab as a preventative treatment for respiratory syncytial virus was associated with a shorter length of hospital stay, a California study showed.

Hospital charges for respiratory syncytial virus (RSV) also increased at a slower pace than for other causes of infant hospitalization, based on a retrospective analysis of California discharges among 3,443,918 infants less than 1 year of age.

The data provide real-world evidence about the impact of palivizumab (Synagis) in the community since its approval in 1998 based on one company-sponsored study, said Dr. Andrew Racine, chief of the general pediatrics section at Albert Einstein College of Medicine in New York City.

"This is important for the following reason: The U.S. sales of palivizumab have gone from about $225 million dollars in 1998 to over $1.5 billion dollars in 2007," he said. "We're using a lot of this; we might as well know if it's effective."

Palivizumab costs about $900 a dose, with most at-risk children receiving five doses as prophylaxis. There is no treatment for RSV.

VITALS

Major Finding: The mean length of stay for RSV fell 13% after the introduction of palivizumab, versus a decrease of 3.4% for other causes of infant hospitalization.

Data Source: Retrospective cross-section comparison of two time periods.

Disclosures: Dr. Racine reported no conflicts or external study support.

Dr. Racine cautioned that the data are from a single state and were not stratified by risk categories for RSV. In addition, the findings were based on an intent-to-treat analysis and thus may not reflect whether patients actually received the medication. The researchers used data from the California Patient Discharge Database and individual level hospitalization records to compare length of stay and hospitalization costs among infants less than 1 year of age during two time periods—before (1995-1997) and after palivizumab (2005-2007).

The mean length of stay for RSV hospitalizations fell 13% from 3.95 days before palivizumab to 3.43 days after the drug. This compares with a decrease of 3.4% for non-RSV hospitalizations, which went from 3.2 days to 3.09. The difference was statistically significant at a *P* value less than .001.

Median hospital charges in constant 2007 dollars for an RSV diagnosis increased 20% from $16,060 to $19,390 after palivizumab, while non-RSV charges rose 59% from $11,901 to $18,857 over the two periods. Again the difference was significant at a *P* value equal to .001.

Session moderator Dr. Esther Chung, of Thomas Jefferson University Hospitals in Philadelphia, said that factors besides length of stay could be driving down RSV hospitalization costs.

Dr. Racine said that lower use of albuterol, corticosteroids, and imaging studies also may have occurred during the second time period, but that these data were not examined and that his own "heartbreaking" experience suggests that these practices continue.

"There are a lot of things we are still doing to these children with this condition that are completely unnecessary and costly," he said.

A study led by Dr. Caroline B. Hall, whose earlier work led to the approval of palivizumab, reported that 3% of 355 outpatients with confirmed RSV infection received an RSV diagnosis, with 20% of these children diagnosed with bronchiolitis. The researchers estimated that RSV infection results in 1 of 334 hospitalizations among children under age 5 (N. Engl. J. Med. 2009;360:588-98). ■