The Cardiovascular and Renal Advisory Panel of the Food and Drug Administration (FDA) met April 9 to 10, 1998, to discuss the safety and effectiveness of inhaled nitric oxide and the platelet IIb/IIIa inhibitor tirofiban.

**Inhaled Nitric Oxide**

Because there are currently a large number of individual investigator Investigational New Drug studies (INDs) for the use of inhaled nitric oxide (INO) in both neonates and adults, the panel met to review what is known about the safety and effectiveness of INO, to discuss the need for further clinical trials, and to consider the goals and designs of any future trials. The panel had recommended in 1995 that the efficacy of INO should be measured by clinical outcomes such as death, use of extracorporeal membrane oxygenation (ECMO), neurological status, and bronchopulmonary dysplasia rather than by improvements in systemic oxygenation. At the last meeting, it was generally agreed that similar standards for drug approval should be used in children and adults, although studies using only mortality as an outcome may currently not be feasible in children on the basis of both the large number needed for a definitive mortality trial and current practice. However, the committee thought that mortality should be included as an outcome along with the use of ECMO and measures of neurological status and bronchopulmonary dysplasia. Trials were presented that showed a marked improvement in oxygenation in the majority of neonates with hypoxic respiratory failure but no benefit on mortality. Although there was a decrease in the use of ECMO in the INO group, no other short-term measures of outcome were improved. The committee agreed that a decrease in the use of ECMO as a reflection of clinical failure of therapy could be the basis for approving INO, but there was concern about the considerable variability in the criteria for the use of ECMO. Some follow-up data are available at 12 and 18 months that do not suggest any major safety problems, but longer follow-up data are scant. Concerns about long-term mutagenesis, neurological problems, and oxidant lung injury remain, and long-term follow-up of all patients in these randomized trials was strongly encouraged. On the basis of these data, the committee believed that it was ethical to continue randomized trials of INO.

**Tirofiban**

Three randomized, blinded, controlled trials (PRISM-PLUS [Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms], PRISM [Platelet Receptor Inhibition for Ischemic Syndrome Management], and RESTORE [Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis]) that included patients with acute coronary syndromes (unstable angina and non–Q-wave infarction) formed the basis for an efficacy claim. In all 3 trials, aspirin was given to all patients. PRISM enrolled 3232 patients comparing tirofiban with heparin. The primary end point was a composite of reduction in new myocardial infarction, additional analyses suggested that this benefit was maintained at 180 days.

PRISM-PLUS included 1915 patients randomized to tirofiban alone, tirofiban plus heparin, or heparin alone. Angiography was not to be performed in the first 48 hours or until an end point was met. The tirofiban-alone arm was aborted early when an interim analysis suggested excess mortality. The primary end point, a composite of death, new myocardial infarction, or refractory ischemia at 7 days, was decreased from 13% to 10%. The dose in PRISM and PRISM-PLUS was fixed at 0.6 μg·kg⁻¹·min⁻¹ over 30 minutes followed by 0.15 μg·kg⁻¹·min⁻¹, or 0.4 μg·kg⁻¹·min⁻¹ when given with heparin, after results of initial dose-ranging clinical trials were reviewed. PRISM-PLUS included 1915 patients randomized to tirofiban alone, tirofiban plus heparin, or heparin alone. Angiography was not to be performed in the first 48 hours or until an end point was met. The tirofiban-alone arm was aborted early when an interim analysis suggested excess mortality. The primary end point, a composite of death, new myocardial infarction, or refractory ischemia at 7 days, was decreased from 13% to 10%. The dose in PRISM and PRISM-PLUS was fixed at 0.6 μg·kg⁻¹·min⁻¹ over 30 minutes followed by 0.15 μg·kg⁻¹·min⁻¹, or 0.4 μg·kg⁻¹·min⁻¹ when given with heparin, after results of initial dose-ranging clinical trials were reviewed. PRISM-PLUS included 1915 patients randomized to tirofiban alone, tirofiban plus heparin, or heparin alone. Angiography was not to be performed in the first 48 hours. Angiography was not to be performed in the first 48 hours.
48 hours or until an end point was met. There was a reduction in end-point events at 48 hours, from 5.6% to 3.8% ($P=0.014$). This result was primarily driven by a decrease in refractory ischemia, and the decrease in events was not significant at either 7 or 30 days, although there was still a similar trend. PRISM showed no increase in mortality with tirofiban alone as was seen in PRISM-PLUS. This study was judged to be somewhat weaker than the usual successful clinical trial.

RESTORE randomized 2141 patients with acute coronary syndromes undergoing PTCA and/or atherectomy within 72 hours of the onset of symptoms. The loading dose was 10 $\mu$g/kg of tirofiban over 3 minutes given when the guidewire was over the lesion, with a maintenance dose of 0.15 $\mu$g · kg$^{-1}$ · min$^{-1}$. The primary end point was a composite of death, new myocardial infarction, and repeat interventions for recurrent ischemia at 30 days. This end point was not significant ($P=0.169$); however, there was a non-protocol-specified analysis at 2 and 7 days with a significant reduction in events ($P=0.003$ and $P=0.022$, respectively). Although not positive, this study was thought to support the results of PRISM and PRISM-PLUS. There was a small increase in the risk of major bleeding, which was thought to be acceptable. Given the totality of the data in these 3 studies, all with similar patients and at similar doses, the committee recommended by 9 to 1 vote that tirofiban be approved as an adjunct to heparin and aspirin for patients with acute coronary syndromes with or without the use of PTCA.
Safety and Effectiveness of Inhaled Nitric Oxide and Tirofiban for Acute Coronary Syndromes: A Report From the Cardiovascular and Renal Advisory Panel of the Food and Drug Administration
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