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Anaphylaxis and Hypotension after Administration of Peginesatide

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TO THE EDITOR: Anemia in patients who have chronic kidney disease and are undergoing dialysis is treated with erythropoiesis-stimulating agents (ESAs).[1] In 2012, the Food and

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Drug Administration approved peginesatide, an ESA that is administered monthly to such patients.[2,3]

In July 2012, a large dialysis organization with 2100 centers in the United States initiated a pilot introduction of peginesatide that included concurrent evaluation of the efficacy and safety of peginesatide and the logistics of administering it. Work groups established systems for evaluating clinical conditions, dosages of the drug, logistics of administration, and review of the efficacy and safety of the product. Personnel at each site were educated about the mechanism of action, pharmacokinetics, storage, handling, and dosing of the drug. The manufacturer provided site specialists. Although registration trials revealed no new toxic effects, by September, eight cases of anaphylaxis and hypotension among patients in the pilot initiative were reported, including two deaths from cardiorespiratory causes and three grade 4 anaphylaxis and hypotension events. In December 2012, the manufacturer updated the product label with a warning that serious allergic reactions, including anaphylaxis reactions and hypotension, may occur in patients who receive peginesatide.[4]

Interim analyses of the pilot initiative showed strong results with respect to achieved hemoglobin levels, decreased iron utilization, and low overall toxicity. In February 2013, the pilot initiative was expanded to include patients who had chronic kidney disease and were undergoing dialysis at 348 centers. On February 11 and 12, field staff reported three fatal cardiorespiratory arrests and two episodes of grade 4 anaphylaxis and hypotension at 4 of these centers. No new patients began to receive peginesatide after February 12, pending analysis of the pilot initiative.

Between July 2012 and February 2013, a total of 61,482 doses of peginesatide were administered to 19,540 patients at 348 centers (Fig. 1). At a total of 19 centers, severe anaphylaxis and hypotension developed in 5 patients, who died from cardiorespiratory arrest in an ambulance or at nearby hospitals; 6 patients had grade 4 anaphylaxis and hypotension; and 17 patients had grade 3 anaphylaxis and hypotension. Symptoms of anaphylaxis began a median of 3.5 minutes after administration of peginesatide (range, 0 to 28.0 minutes). There were 1.4 anaphylaxis and hypotension events per 1000 patients. On February 22, 2013, after the review of data from the pilot initiative, the dialysis organization discontinued administration of peginesatide. On February 23, the manufacturer voluntarily recalled the drug.

The cause or causes of these episodes of anaphylaxis and hypotension have not been defined. All patients received peginesatide from multiple-use vials that contained preservatives, whereas in preapproval trials, patients received the drug from single-use vials.[2,3] Prior exposure to ESAs, demographic characteristics, and coexisting device or drug sensitivities have not been associated with the mechanisms of toxicity.

The recognition of anaphylaxis and hypotension resulted in removal of peginesatide from the market. Peginesatide was effective in maintaining hemoglobin levels and was convenient to administer in 19,512 of the 19,540 patients in the pilot initiative. Physicians have been able to continue using other drugs associated with anaphylaxis by administering test doses followed by monitoring before administering full doses or developing formulations that are

not associated with anaphylaxis.[5] Finally, new peptide and protein therapeutic agents have been associated with immediate hypersensitivity and might be candidates for pilot initiatives with concurrent observational analysis such as the pilot initiative involving peginesatide.

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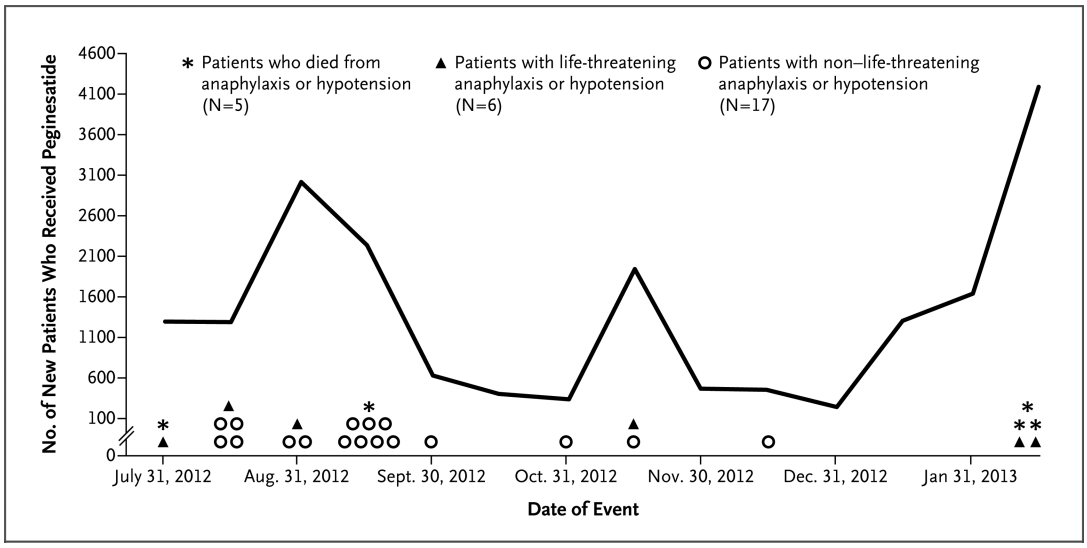

Figure 1.

Fatal, Life-Threatening, and Non–Life-Threatening Occurrences of Anaphylaxis and Hypotension in Patients Who Received a First Dose of Peginesatide.

Deaths and life-threatening and non–life-threatening events were reported to the Food and Drug Administration.