Correspondence

To the editor:

Human recombinant factor IX: safety and efficacy studies in hemophilia B patients previously treated with plasma-derived factor IX concentrates

Roth et al1 recently published the results of clinical studies to evaluate the safety and efficacy of recombinant human factor IX (rFIX; brand name BeneFIX) in previously treated patients (PTPs) with severe or moderate hemophilia B. These studies were conducted in North America and Europe from February 1995 to April 1999 and are part of the 3 pivotal clinical studies on which the marketing authorization for BeneFIX is based.

In June 2001, the Committee for Proprietary Medicinal Products (CPMP) expressed concern, following the outcome of a Good Clinical Practice (GCP) inspection conducted on behalf of the European Agency for the Evaluation of Medicinal Products (EMEA) about the conduct of these studies and the reliability of their outcome.

Therefore, the author of this letter wishes to bring to the reader’s attention the following information regarding rFIX, which was originally published by the EMEA on its website.2 At the same time, the CPMP asked the marketing authorization holder (Genetics Institute of Europe BV) to bring the EMEA-published information to the attention of prescribing physicians.

The outcome of the GCP inspection of the 2 published studies revealed GCP deficiencies that cast doubts on the reliability of the clinical data. An independent audit of the 3 pivotal clinical studies, commissioned by Genetics Institute of Europe BV, confirmed the GCP deficiencies but found the data to be real and representative of the population studied.

rFIX has been commercially available in Europe since 1999 and in the United States since 1997. Postmarketing data accumulated since then from physicians treating hemophilia B patients support the safety and efficacy profile of rFIX. The CPMP considers that the benefit/risk balance of rFIX for the treatment and prophylaxis of bleeding in PTPs with hemophilia B is positive, based on the data presently available. However, the data are insufficient to be certain of the frequency of some adverse drug reactions, especially those linked to inhibitor formation and to allergic reactions. Because of these concerns, there is a need for enhanced surveillance of new patients receiving rFIX. This intensive postmarketing surveillance will include a registry for all new patients treated with rFIX in Europe. Patients already treated with rFIX may continue their therapy. However, patients who experience suspected adverse drug reactions should be monitored carefully and the risks/benefits of continued treatment should be evaluated.

The recommendation to check for the presence of an inhibitor when a lack of efficacy is observed at the recommended dose was reinforced. Additionally, a recommendation to switch patients to another factor IX product if doses greater than 100 IU/kg have been repeatedly needed during routine prophylaxis or treatment, even if an inhibitor is not detected, has been implemented by the marketing authorization holder.

At the request of the CPMP, 2 new clinical trials will be conducted by Genetics Institute of Europe BV in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)3 and the recent CPMP Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and IX products (CPMP/BPWG/1561/99).4 Genetics Institute of Europe BV is in the process of implementing corrective actions to address the deficiencies found in the GCP inspection.

Manfred Haase

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M.H. is Chairman of the CPMP Ad Hoc working group on Blood Products (BPWG).

References


Response:

Human recombinant factor IX: safety and efficacy studies in hemophilia B patients

Wyeth Pharmaceuticals is committed to providing physicians and patients with the most comprehensive safety and efficacy information available about rFIX (commercially distributed as BeneFIX). Dr Haase’s letter is a valuable reminder to the readers of Blood of the importance of this information. The company continues to work diligently with the Committee for Proprietary Medicinal Products (CPMP) to provide the necessary and appropriate data to support the safety and efficacy of rFIX. Together with the European regulatory agency, we have sent specific information on the rFIX clinical trial data collection process and on modifications to the rFIX Summary of Product Characteristics (SPC) to the community through letters to hemophilia physicians and through contact with hemophilia advocacy organizations.

To address the concerns of the CPMP, the company has implemented 2 initiatives. The first is the establishment of a prospective registry of all new hemophilia B patients in the European Union beginning treatment with rFIX to gather additional safety information on rFIX in the usual practice setting. The
second is the initiation of new clinical trials to obtain more data on the safety and efficacy of rFIX. One clinical trial will study rFIX in children younger than 6 years of age with severe hemophilia B, including both previously treated patients and previously untreated patients. The other trial will study rFIX in previously treated patients with severe or moderately severe hemophilia B who are 12 years and older. Both trials were designed taking into consideration the CPMP Guidelines for the Investigation of Recombinant Factor VIII and Factor IX (CPMP/BPWG/1561/99 [October 2000]).

Wyeth Pharmaceuticals and Baxter Healthcare—the exclusive distributor of BeneFIX in the European Union—encourage physicians to support efforts to collect additional safety and efficacy information.

Harold Marder and Bruce M. Ewenstein

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Response:

The recombinant factor IX clinical investigator group’s response to Dr Haase

As academic hematologists and clinical investigators, we depend on the integrity and validity of clinical research data to guide our decisions and are committed to generating reliable data of the highest quality. Furthermore, we are committed to publishing the outcomes of our research, especially when they significantly contribute to advancing our clinical knowledge and improving the quality of health care and medical practice. Regulatory agencies, such as the European Agency for the Evaluation of Medicinal Products (EMEA), are also dependent on the results of well-conducted studies to make their decisions. We thank this agency for scrutinizing data to ensure that its objectives can be achieved.

We congratulate Wyeth Pharmaceuticals for its courage to sponsor expensive clinical research in rare diseases, especially in hemophilia. These investigations have required a multinational effort and have included intricate and complex clinical protocols in both the inpatient and outpatient settings. The investigators who participated in these trials believe that the administrative oversight recovered by the EMEA-commissioned Good Clinical Practice (GCP) inspection do not compromise the scientific integrity or robustness of the data that were generated by these studies.

We are reassured by independent audits of the data, as cited in Dr Haase’s letter, because these audits confirm that the published data are real and representative of the population studied. Dr Haase’s letter also indicates that the postmarketing data continue to support our published conclusions regarding the safety and efficacy profile of human recombinant factor IX (rFIX).

Lastly, we are reassured by the fact that in light of the findings of the GCP inspection, the Committee for Proprietary Medicinal Products (CPMP) still considers that the benefit/risk balance of rFIX for the treatment and prophylaxis of bleeding in previously treated patients (PTPs) with hemophilia B is positive. We directly acknowledged in our publications that additional studies are required to define the true risk of immune responses to rFIX, including the development of inhibitors and allergic reactions, and we support the need for enhanced surveillance of new patients receiving rFIX. We must emphasize to the readership of Blood that the publications generated by these clinical trials were based on valid data generated and interpreted in an objective manner. These reports accurately reflect the investigators’ favorable clinical experiences with the study patient populations as described.


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References


To the editor:

ETO sequence may be dispensable in some AML1-ETO leukemias

Acute myeloid leukemia (AML) is a heterogeneous disease, with individual cases showing variability in clinical presentation, blast-cell morphology, therapeutic response, and long-term prognosis. One of the most common cytogenetic abnormalities described in AML is t(8;21)(q22;q22) found in 10% to 15% of cases.1 As a consequence of the chromosomal translocation, 5 exons of the AML-1 gene are fused to nearly the entire coding sequence of the ETO gene, generating an easily detectable polymerase chain reaction (PCR) product of a constant size (260 bp), corresponding to an in-frame fusion of AML1 exon 5 to ETO exon 2. This novel chimeric gene, AML/ETO, encodes a fusion protein with a primary inhibitory role in the normal hematopoietic differentiation program.

Adult patients with de novo–diagnosed AML enrolled in the Spanish Estudi i Tractament de Leucèmies Agudes i Mielodisplàssies (CETLAM) 99 protocol were tested for the presence of chimeric AML1-ETO and CBFβ-MYH11 mRNA using the BIOMED-1 protocols. Briefly, 1 μg of RNA obtained from fresh leukemic bone marrow was retrotranscribed into cDNA using random hexamers. RNA quality assessment was carried out with 5 μL of cDNA in a 1-step PCR amplification of the normal ABL.