EMA Workshop Focuses on Viral Safety of Plasma-Derived Medicinal Products WITH RESPECT TO HEV

BY MARY CLARE KIMBER

On October 28-29, 2014, PPTA and member companies participated with regulators, clinicians, and industry in a closed “Workshop on viral safety of plasma-derived medicinal products [PDMPs] with respect to hepatitis E virus [HEV]” organized by the European Medicines Agency (EMA) in London.

It was intended to provide the basis for deciding what further action may be needed, including possible updates of current regulatory guidance and/or development of a new position or reflection paper specifically on the viral safety of PDMPs with respect to HEV. PPTA Pathogen Safety Steering Committee (PSSC) members Thomas R. Kreil (Chair, Baxter BioScience), Albrecht Gröner (CSL Behring), and Rodrigo Gajardo (Grifols) presented the results from studies on the inactivation/removal of HEV, followed by PPTA perspectives on risk assessment for PDMPs and implications for warning statements.

BACKGROUND

HEV, a zoonotic disease present in pig populations around the world, has been transmitted by transfusion of blood components, yet not by PDMPs, although HEV has been detected in plasma for fractionation. Information derived from HEV-associated complications in transfusion and transplantation was reviewed during workshop discussions, as well as the severity of clinical consequences of infection.

ARE PDMPS SAFE WITH RESPECT TO HEV?

Attending regulators stated that there has not been any transmission of HEV through PDMPs. Not a new virus, HEV has been present in e.g. the EU for decades, and thus transmissions should have been observed if there was a potential risk. However, regulators cautioned that HEV infection may be under- and mis-diagnosed, as patients with symptoms are not always tested for HEV, and thus transmissions may be missed.

Based on the virus reduction data presented, attending patient groups [International Patient Organization for Primary Immunodeficiencies (IPOPI), European Haemophilia Consortium (EHC) / World Federation of Hemophilia (WFH), European Liver Patients Association (ELPA)] stated that PDMPs are safe with respect to HEV. EHC/WFH did propose to introduce screening for blood donors to protect hemophilia.
patients that do not have access to recombinant therapies and rely on transfusion products.

**WHICH STEPS ARE EFFICIENT TO REMOVE/INACTIVATE HEV (WHICH MODEL VIRUSES CAN BE USED)?**

There are open questions that need to be addressed before any final conclusion on the efficacy of certain inactivation/removal steps for HEV can be made. Although there is certain confidence based on the available data, particularly with model viruses, only data with HEV itself will be able to confirm today’s assumptions. There is a need for more data generated with HEV as the virus of concern, but the establishment of test systems is difficult, particularly the generation of high titer supernatants.

**ARE MORE VIRUS REDUCTION DATA NEEDED?**

Since there are still many open questions, regulators were adamant that more studies are needed, although regulators may not require data from each company on efficacy of every reduction step in clearing HEV at this stage. While data presented were generally consistent, conflicting data on certain details presented raised some doubts whether the underlying mechanisms are sufficiently understood.

EMA has not required HEV NAT testing for PDMPs, even if rare pools may contain a low viral burden, based on converging evidence from model and target virus reduction studies that support final product safety margins.

Of note, IPOPI was confident about the safety of PDMPs and cautioned that safety measures should be balanced against availability. Unnecessary loss of plasma and unwarranted incurrence of costs should be avoided for products with an excellent record of safety.

**DO SERUM HEV ANTIBODIES NEUTRALIZE THE VIRUS?**

Available data indicate that the neutralization capacity of HEV antibodies may be limited and of lower avidity. The observation may be explained by preliminary evidence that the non-lipid enveloped HEV may be coated with lipids under certain circumstances, which may render neutralization less effective.

**ARE RISK ASSESSMENTS AND/OR WARNING STATEMENTS NEEDED?**

During the workshop there was general agreement that adding HEV to the warning statement for hepatitis A (HAV) and parvo virus B19 (B19V) in the EMA guidance would not be appropriate at this time, in that the general statement in the current guidance covers any theoretical HEV risk: “the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.” Noting that there have been no transmissions of HEV by PDMPs reported to date, although

“Available data indicate that the neutralization capacity of HEV antibodies may be limited and of lower avidity. The observation may be explained by preliminary evidence that the non-lipid enveloped HEV may be coated with lipids under certain circumstances, which may render neutralization less effective.”

HEV has been circulating in the human population for a long time, regulators indicated that adding product-specific statements on HEV reduction measures would only enable marketing based on a product attribute of theoretical value.

**NEXT STEPS**

Regulators concluded that more data are needed before any final decision-making process can commence. For now, regulatory measures, such as e.g. incentivizing NAT testing or adding warning statements, would not improve product safety. As a first step, EMA plans to publish a workshop report and reflection paper subject to consultation with stakeholders. PPTA will continue to engage EMA and other regulators, as well as the patient community, to ensure that any policy developments rationally reflect ongoing research and understanding of viral safety of PDMPs with respect to HEV.

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