Working Together for the Future of Human Immunoglobulin Therapy

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IMMUNOGLOBULIN THERAPY

Polyclonal human immunoglobulin (IgG) is used as a replacement therapy (IgG-RT) in individuals with primary immunodeficiency (PI) diseases who display a deficiency of the humoral immune system due to abnormalities in the synthesis and/or function of antibodies. IgG-RT represents a unique, lifesaving, and life-long standard treatment for affected individuals. It offers the best outcomes when initiated early in life and includes treatment with the highest dosing of medicine within the recommended range. IgG therapies are made from pools of Source or recovered plasma collected from at least 1,000 healthy donors who are rigorously tested to ensure safety related to bloodborne pathogens.

WORKSHOP

Since the 1960s, the U.S. Food and Drug Administration (FDA) has required the potency of each IgG product lot to be tested for antibody specificities against the measles virus, poliovirus, and diphtheria to ensure functionality and lot-to-lot consistency. More than a half century has passed since this regulation was put in place, and a few issues have become apparent: 1) declining levels of measles-neutralizing antibodies in IgG lots related to donor vaccination; 2) the impact of approaching total eradication of poliovirus infections; 3) the relevance of the current potency tests to the clinical outcomes in PI patients on IgG-RT and whether modern and more appropriate potency tests should be considered in the future. In November 2017, a workshop titled “Immune Globulin Potency in the 21st Century” was

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organized through the collaborative efforts of the FDA, PPTA, the National Institute of Allergy and Infectious Diseases, and the Immune Deficiency Foundation (IDF). This workshop was an important event embraced by IgG manufacturers, regulators, the patient community, physicians, and researchers from governmental institutions and academia. Presentations at this event were recorded with support from the IDF, and transcripts are available on the FDA website.[1]

A SUPPLEMENT TO *TRANSFUSION*

After the workshop, the FDA and PPTA collectively worked with speakers to publish scientific work relevant to the workshop in a peer-reviewed journal (published December 2018). Our thanks go to Richard Kaufman, M.D., (the editor of *Transfusion*), who accepted our proposal and to the publisher and staff who worked tirelessly on making sure the supplement was published, "A Supplement to *Tranfusion*," Volume 58, Issue S3) and made accessible to readers by Open Access (financial support provided by the FDA and PPTA).[2] In the supplement, Dorothy Scott, M.D., from the FDA Center for Biologics Evaluation and Research (CBER) offered a comprehensive assessment of all aspects of the workshop. IDF President John G Boyle also provided many valuable comments.

The supplement covers several topics, one of which is related to the potency testing of IgG products as a measure of their functionality against the measles virus. This issue has relevance for IgG manufacturers as well as individuals with primary humoral immunodeficiency who rely on lifesaving and life-long IgG-RT. Industry investigators showed that titers of measles-neutralizing antibodies in plasma donors steadily declined since the introduction of vaccination against measles infection. They also established that lowering the lot release specification for measles neutralizing antibody from 0.48x to 0.30x CBER Standard lot 176 (16.5 percent) for IgG products would still be sufficient to protect patients against measles.

Another topic addresses new challenges the industry is facing in view of the global eradication of wild-type poliovirus through the World Health Organization efforts. The main issue is related to addressing the highest level of safety measures in the laboratories handling the poliovirus. New developments in genetic engineering research offer a possible solution to the industry to address this concern while continuing to perform potency testing of IgG products for poliovirus-neutralizing antibodies. A few articles explore possibilities for new and more advanced potency assays, instead of those currently in place, that could be considered in the future as more appropriate for clinical outcomes in individuals with primary humoral immunodeficiency.

The editors' goal would not have been achieved without the contribution of reviewers who were represented by industry investigators, regulators, and researchers from academia. PPTA believes this supplement will serve as a reference guide for future IgG products — and as a starting platform for discussions of appropriate potency tests relevant to clinical outcomes in individuals with primary antibody deficiencies.

LETTER

An important outcome of the workshop came in the form of an FDA decision to issue a recommendation "Letter to Immune Globulin (Human) Licensed Manufacturers: Option to Lower Lot Release Specification for Required Measles Antibody Potency Testing," dated Nov. 5, 2018.[3] This letter informs manufacturers that under 21CFR 640.104(b)(2), CBER sets the minimum specification for measles neutralizing antibody levels in Immune Globulin products as 0.36 x CBER Standard lot 176 (16.5 percent). It also advises adding labeling to the prescribing information that contains corresponding recommendations for dosing of patients with primary humoral immunodeficiency who have been exposed, or are likely to be exposed, to measles. •

References:

1. Transcripts to the Workshop "Immune Globulin Potency in the 21st Century." November 8-9, 2017. Available online at: https://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm568419.htm
2. A Supplement to *Transfusion*. Vol. 58, No. S3, December 2018. Available online at: https://onlinelibrary.wiley.com/toc/15372995/2018/58/S3
3. U.S. Food and Drug Administration (FDA). Letter to Immune Globulin (Human) Licensed Manufacturers: Option to Lower Lot Release Specification for Required Measles Antibody Potency Testing. November 5, 2018. Available online at: https://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/UCM626655.pdf?utm_campaign=What%27s%20New2018-11-6&utm_medium=email&utm_source=Eloqua