Measles Antibody Levels in U.S. Immune Globulin Products

Summary of Blood Products Advisory Committee
August 16, 2007

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Issue

FDA sought the advice of the Committee on a proposal to lower the minimum recommended lot release titer for measles antibodies in Immune Globulin Intravenous (Human) (IGIV) and Immune Globulin Subcutaneous (Human) (IGSC).

Background

- Measles antibody titers serve as a potency test for lot release of all immune globulins licensed in the U.S.
- Measles antibody levels in products have been declining in recent years
- Failure of potency testing would result in rejection of Lot(s) with a negative impact on product availability for Primary Humoral Immune Deficiency Diseases (PIDD)
- CBER proposed to lower the minimum measles antibody titer of IGIV and IGSC to levels expected to be effective in pre-exposure protection in patients with PIDD.
- Immune Globulin Intramuscular (IGIM) is indicated for post-exposure protection in normal individuals and will be considered separately.

Lot Release Tests: Regulatory Requirements

"Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that …drug products conform to appropriate standards of identity, strength, quality, and purity."

21 CFR 211.160(b)

Potency Testing for Immune Globulins

- Rationale: Assurance of strength and quality
- What do specifications provide?
  - Measure of lot-to-lot consistency
  - Assurance of product integrity (tests that measure antibody function and titer)
  - Measure of activity that is relevant to the indication – for patients with PIDD

Current U.S. Immune Globulin Product Potency Tests

- Antibodies to measles, diphtheria, polio (type 1, 2, or 3), and Hepatitis B surface antigen

- All the above tests except anti-HB_s are neutralization assays; anti-HB_s provides additional assurance of viral safety

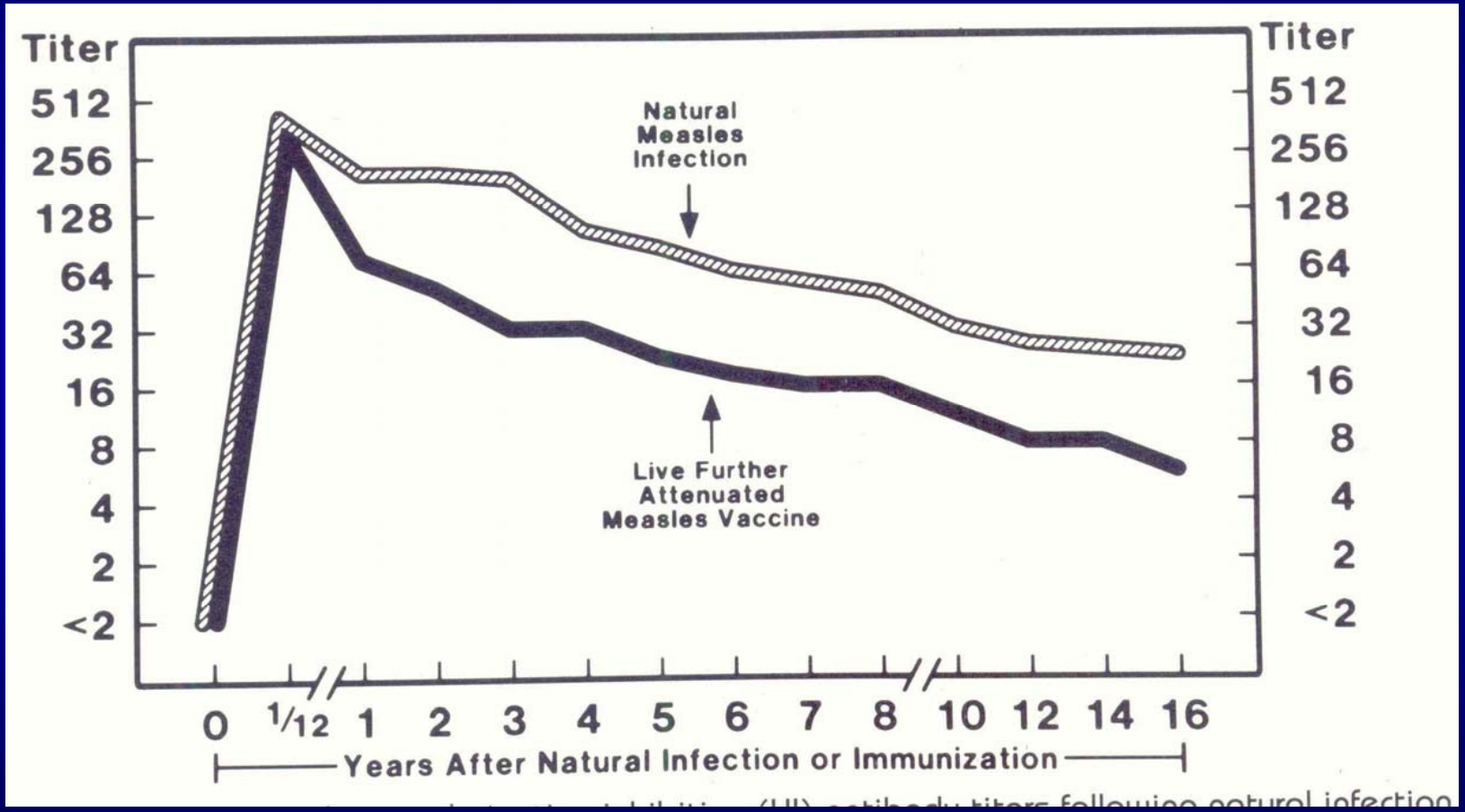
IGIV/IGSC and Measles Antibodies

- Measles antibody levels are a standard measure of potency for U.S. Immune Globulins
  - Historically important specificity
  - Potency tests are available and correlate with protection in normal subjects
- Measured by bioassay – hemagglutination inhibition or neutralization
- Declining antibody levels observed in products over past several years

Why Are Anti-Measles Antibodies Declining in Donors?

- Natural infection results in higher antibody levels
- Proportion of vaccinated (as opposed to naturally infected) donors is likely to be increasing
  - Vaccine licensed in 1963; implemented over ensuing years
  - Naturally infected population of donors aging
    - More deferrals
    - Fewer donors

Natural Infection Induces Higher Titer Antibodies Over a Longer Period Than Vaccination



Measles Vaccine, Lauri Markovitz and Samuel Katz, in Vaccines, Second Edition, edited by Stanley Plotkin and Edward Mortimer, Jr., WB Saunders, Philadelphai PA, 1994

Measles Potency Test for Immune Globulins

- 1944 – Demonstration of measles prophylaxis by IGIM (Stokes, J. Clin. Invest. 23:531-40)
- c. 1953 Minimum Requirements for Immune Serum Globulin (ISG) “several lots should be effective in prophylaxis of measles”*
- As measles potency tests became available, CBER developed standards

* 1953 ISG (Human) Minimum Requirements
US DHEW, NIH

CBER Measles Antibody Potency Standard

- 1961: Lot 1 standard (serum from immunized primates)
  - ISG should be 0.25 x standard Lot 1
  - The cutoff was established based on a study of 60 ISG lots, considered potent for measles prophylaxis. The cutoff permitted future lots to pass specification with a probability of 95%.
- 1971: replacement of Lot 1 with Lot 175
- 1992: replacement of Lot 175 with current Lot 176
  - Current lot release criteria: lots should have at least 0.6 x potency compared to Lot 176, when compared at the same IgG concentration
- 2007-8: planned replacement of lot 176 with lot 177

Clinical Issues - Measles Prophylaxis in PIDD Patients

- Measles incidence is rare in the U.S. – only 66 confirmed cases in 2005 (CDC)
- Reports of measles infection in PIDD patients are rare
  - Lack of exposure to measles and/or protection due to treatment with IgG
- Last major outbreak in the U.S. was 1989-91 with > 55,000 cases reported (prior to 2 dose vaccination)
- Since 2001, measles outbreaks in the U.S. are rare and usually attributable to exposure outside of the U.S.

Clinical Issues (contd.)

- Measles remains an important pathogen worldwide
- 21% of disease-related deaths in children < 5 years of age
- Antibodies are needed to prevent infection while measles virus clearance depends mainly upon CD8+ T cells.
- PIDD patients, especially those with combined humoral and T cell deficiencies, are susceptible to severe measles disease.

Protective Titer Against Measles Infection

- Serum titer of 120 mIU/mL – protective against clinical disease in healthy, vaccinated individuals
- ≥ 1052 mIU/mL – protective against infection

- Lack of published pharmacokinetic data analyzing measles titer in IGIV product administered, and the consequent trough level measles neutralizing antibody, in PIDD patients.

- Protective level in PIDD unknown
  - more than 100 distinct PIDD syndromes, therefore, protective measles antibody levels may vary as well.

* *Chen, 1990 JID 162:1036

Rationale for New Measles Antibody Specification:

- IGIV dose for most PIDD patients is 200-800 mg IgG/kg, given every 3-4 weeks.
- Trough measles antibody titers for patients receiving 400 mg/kg IGIV every 4 weeks is estimated to range from 250 – 718 mIU/mL, based on CBER testing of lots and calculated trough levels*
- The calculated theoretical minimum anti-measles antibody potency of IGIV, given at 200 mg/kg, to achieve a trough level of 120 mIU/mL, would be 1200 mIU/mL or 0.48 x CBER Standard Lot 176.

* Audet et al, JID 194: 781-9, 2006.

Possible Strategies to Address Declining Measles Antibody Titers in Immune Globulin Products

- Lower the recommended measles lot release specification titer for IGIV and IGSC if there is assurance that minimally protective titers are present
- Revaccinate plasma donors in an attempt to increase antibody levels
  - Likelihood of achieving substantially higher and durable levels is estimated to be low in adults

Questions for the Committee:

1. Do Committee members concur with the FDA proposal to lower the minimum measles antibody specification for IGIV and IGSC from 0.60 x CBER standard, to 0.48 x CBER standard?

Votes

Yes: 13 No: 1

Questions (contd.)

2. CBER is considering requesting additional studies to confirm that PIDD patients will achieve trough levels of measles antibodies above 120 mIU/mL if treated with IGIV and IGSC products that meet the proposed revised potency standard of 0.48 x CBER standard. Do the Committee members agree that this information is needed?

Votes

Yes: 13 No: 1

Discussion

Please comment on the need for and feasibility of any alternative strategies that CBER should consider to reduce the likelihood of failed lots of IGIV and IGSC based on potency testing for measles antibodies in order to ensure availability of product for PIDD patients.

Action Items for Follow Up Based on BPAC Discussions

- Consider requiring testing for relevant antibodies (measles, enterovirus, H. influenzae and S. pneumoniae) and consider requesting that manufacturers indicate actual titers on labels.

- PIDD patients going to areas with endemic measles, should be infused prior to travel, preferably with high titer product.

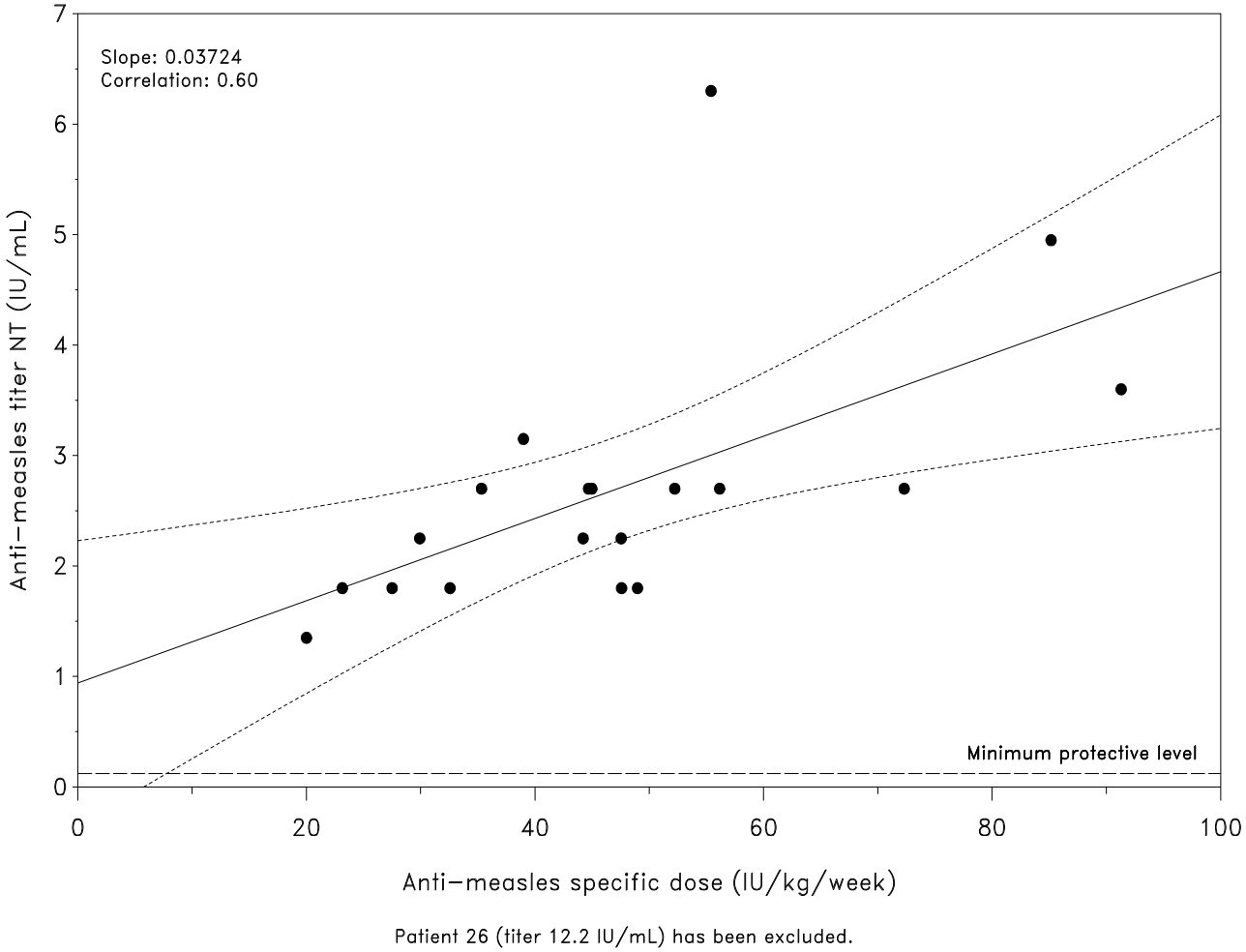
- Education of physicians may be needed so that for PIDD patients going on travel, or in times of measles outbreak, adjustments in therapy can be made to assure that protective titers are achieved.

Other Items for F/U

- If exposed to measles, SCIDs (< 1% of PIDD fall into this category and are usually diagnosed at < 1 year and treated with BMT) and others with profound T cell deficiencies (e.g. HIV infected with very low CD4 counts) should be treated with higher doses to achieve titers that achieve "sterilizing immunity" i.e. > 1000 mIU/mL.

- IGIM was not part of the presentation but needs to be dealt with by FDA.

IGSC – Dose response (NT)*

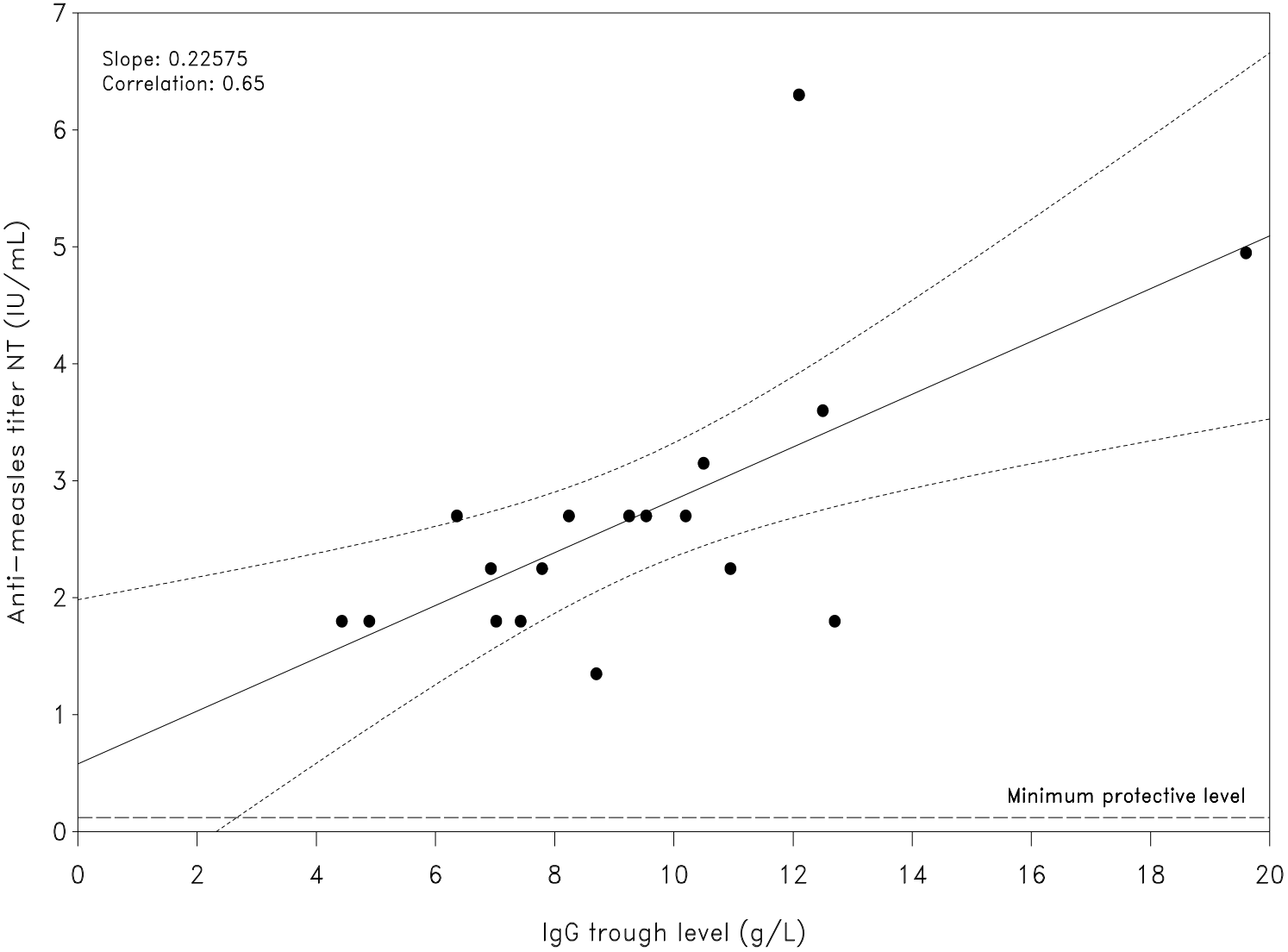


Patient 26 (titer 12.2 IU/mL) has been excluded.

- All patients are well protected
- Mean titer is 3.17 IU/mL
- Good correlation between dose and titer

*Presented by CSL Behring at BPAC 8/16/07

IGSC - anti measles and trough level (NT)*



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