Workshop Summary

Intravenous Immune Globulins in the 21st Century: Progress and Challenges in Efficacy, Safety, and Paths to Licensure

(http://www.fda.gov/cber/minutes/igiv041305t.htm)

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Advisory Committee for Blood Safety and Availability

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IGIV Workshop
April 13, 2005
Lister Hill, NIH Campus

- Cosponsored by FDA and the Immune Deficiency Foundation (IDF)
- Planning Group: IDF (including members of the medical advisory board), FDA, PPTA, CMS
- 18 speakers
- >150 attendees
- Transcripts Posted:

http://www/fda/gov/cber/minutes/igiv041305t.htm

Goals

- To discuss current issues in efficacy and safety of immune globulins
- To examine and analyze results of FDA's 1999 paradigm for IGIV licensure for Primary Immune Deficiency
- To present considerations for licensure of subcutaneous IG
- To generate outcomes that will enhance future safety and efficacy of IGIV products

Unresolved Issues in IGIV Efficacy for PID

- Dosing for infection prevention – frequency, dose needed, and individualized treatment
  - Monitoring
    - IGIV peak
    - Trough
    - AUC
  - Surrogate markers for IGIV efficacy (for trials)
    - Proposal for important antibody specificities that should be achieved at certain levels in patients (R. Stiehm)
  - Clinical outcome measures – what are the relevant parameters?
    - pulmonary function
    - infection frequency
    - antibiotic use

Surrogate Markers for IVIG in PID Patients

1. Trough IgG levels (> 500mg/dL)
2. Trough IgG1, IgG2, and Ig3 levels
3. Antibody Titers to Diphtheria , Tetanus, H. Flu, S. Pneumoniae (5 Serotypes), Hepatitis B , Measles, VZV, CMV
4. Pulmonary Function Tests
5. Acute phase reactants

OPTIONAL: Pharmacokinetics, Functional Ab Assays, X-rays, Other Ab titers

From R. Stiehm, M.D., UCLA, IGIV Workshop April 13, 2005

Unresolved Issues in IGIV Efficacy for PID

- Infections in patients receiving IGIV
  - Better understanding of natural history of PID treated with IGIV is needed
  - End-organ [pulmonary] damage increases infection rate in IGIV-treated patients – how can treatment be improved?
  - Chronic infections (mycoplasma, echovirus, etc.) – can IGIV's selected for high titers or in combination with monoclonal antibodies be therapeutic?
  - Need for early diagnosis to prevent end-organ damage

Conundrum

- Population surveys suggest that PID's affect an estimated 50,000 persons in the U.S. and that they are at least as common as hemophilia (<15,000), cystic fibrosis (30,000), Huntington's Disease (30,000) and phenylketonurea (<18,000).
- However, true incidences will not be known until there is population screening.

From: R. Buckley, M.D., Duke University (IGIV workshop 4/13/05)

The Question of Cost

- Half of all persons with PID's are not diagnosed until they are adolescents or older.
- The cost of late diagnosis is a heavy burden of disease on the patient and often early demise.
- The majority of patients report two or more hospitalizations before diagnosis. The cost of hospitalization of these patients far exceeds what it would cost to screen for the defect and to implement therapeutic or preventive measures.

From: R. Buckley, M.D., Duke University (IGIV workshop 4/13/05)

Screening Proposal

- For PID (not SCID)
  - IgA
  - If IgA low, then measure IgG to rule out agammaglobulinemia
- For SCID
  - Absolute lymphocyte count (cord blood)
  - If low, then assess absolute T cell count

From: R. Buckley, M.D., Duke University (IGIV workshop 4/13/05)

Potential Threats for PID

- West Nile virus
- Smallpox or exposure to family members receiving immunization

New

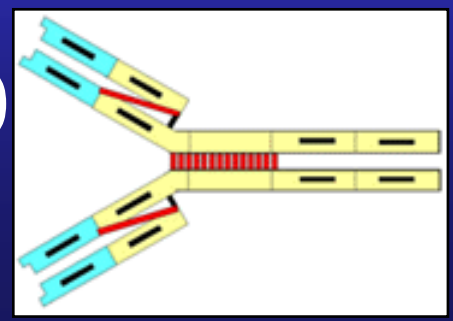
- Varicella
- Measles

Changing Epidemiology

Antibody Titers in IGIV – Sources of Variation

- Donor epidemiology
  - disease exposures
  - vaccination status
  - regional epidemiology
  - vaccination vs. natural immunity
  - new vaccination programs for children, adults

- Manufacturing methods (e.g. IgG3)



Is There a Role for an IGIV Repository?

- Research purposes:
  - Monitoring trends in antibody levels (e.g. measles, WNV, vaccinia, varicella)
  - Assessing emergence in product of potential protection against new pathogens

For Discussion: Proposed IGIV/IG Repository

- 5 random lots/product (20 ml)
- Coded and frozen aliquots (- 70 degrees C)
- Yearly deposits
- Who can request?
  - **Accessibility to FDA, CDC**
  - **Outside investigators**
- Sample blinding/unblinding?)
- FDA research – antibody levels to common and emerging pathogens
- Published information would be coded
- Voluntary program – no requirement to submit samples (as opposed to lot release)

IGIV Efficacy Session Outcomes

- Formation of a working group to address
  - Association of dose and trough levels with clinical outcomes over time
  - Optimization of treatment in patients with end-organ [lung] disease
  - Validation of surrogate markers of efficacy
- FDA working group to generate IGIV repository draft proposal for consideration

IGIV Safety Issues

- Limitations of IGIV clinical trials
  - Products are not compared to each other
  - Clinicians feel that adverse event labeling is difficult to compare among products
  - Clinicians suggest that more standardized ascertainment of adverse events would be useful
  - Post-marketing AE rates in clinically treated population are not known
  - Rare adverse events unlikely to be detected

Models for Surveillance of Adverse Events

- FDA's surveillance via Medwatch (Robert Wise, M.D., MPH, OBE/CBER)
- CDC's Universal Data Collection System (Mike Soucie, Ph.D., CDC)
- Case study: Industry model of active surveillance (Judi Miller, BSc, Octapharma)

Issues in Adverse Event Surveillance in IGIV Recipients

- Advantages of enhanced surveillance
  - Early detection of unusual/severe adverse events permits early intervention
  - Characterization of AE profile and associated underlying factors
  - More complete data
  - Long latency events may be identified
- Hurdles in establishing more effective surveillance for IGIV recipients:Infrastructure, Funding
- Possible Improvements/solutions
  - Patient or Foundation-generated reporting systems
  - Enhanced industry post-marketing surveillance
  - Surveillance in select institutions with PID expertise

AE case studies

- Product withdrawals for increased reports of urticaria/hives/allergic symptoms (D. Baker, M.D., Baxter)
  - Multiple manufacturers
  - Extensive investigation
  - No *in vitro* correlates/no manufacturing correlates
  - Ongoing additional investigations and search for predictors
- Adverse Event and Product Withdrawal – Case Study - Communication to Healthcare Providers and Patients (J. Roberston, Talecris)

IGIV Safety Session Outcomes

- FDA and IDF discussion of feasibility of patient registries for the purpose of active patient-driven surveillance
- Can funding be obtained to enable active surveillance at select institutions?
- Can active surveillance be combined with monitoring of long-term clinical outcomes (as discussed in workshop efficacy session)?

IGIV Licensure

- FDA – Trial design for PID from the March 2000 BPAC reviewed
  - 1996-2002 no new IGIV's licensed
  - 2003-2005: **4 new IGIV products licensed**
- Industry – future of IGIV licensure
  - Secondary immune deficiency labeling possible based on licensure for PID?
  - Can surrogate endpoints be used to decrease efficacy trial time or patient number?
  - Establishing appropriate balance among pre-licensure safety studies and post-licensure active surveillance
  - Harmonization with other authorities on path to approval for non-PID conditions

Final Session Topics

- Subcutaneous IG Licensure for PID
  - FDA current thinking
  - Paradigm for licensure
    - Same efficacy outcomes as for IGIV
    - Considerations – bioavailability based on use of area under the curve as most important PK parameter
- Critical Path – identification of projects
- IGIV Availability
  - Marcia Boyle, Chairman and CEO, IDF: Limited Availability of IGIV for PID patients
  - Follow up information gathering discussions began 4/29/05 (FDA, IDF, PPTA)

Advice and Support THANKS

- Immune Deficiency Foundation, including members of the Medical Board
- Jerry Holmberg, Ph.D., OS
- Office of Blood Research and Review, CBER
- CBER Planning Group (Basil Golding, Jonathan Goldsmith, Dorothy Scott)
- CMS
- PPTA
- ALL of our SPEAKERS
- Rhonda Dawson, Policy Analyst

Critical Path Ideas for Discussion

- Development of surrogate markers to predict infusion-related (and other) adverse events
- Use of surrogate markers to support efficacy (in setting of manufacturing changes, also for licensure)
- Streamlining/improving existing tests for lot release/stability/conformance lots
- Development of paradigms for licensure IGIV for non-PID indications
- We welcome input and identification of specific needs/problems to be solved!