Summary FDA Workshop on Inhibitors

Glenn Pierce MD PhD

WFH Global Forum
Montreal
26-27 Oct 2015
## Disclosures for: Glenn Pierce

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<th>Conflict</th>
<th>Disclosure - if conflict of interest exists</th>
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<td>Research Support</td>
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<td>Director, Officer, Employee</td>
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<td>Shareholder</td>
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<td>Advisory Committee</td>
<td>Alnylam, Intas</td>
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<td>Consultant</td>
<td>BioMarin, Genentech/Roche</td>
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Public Workshop: New Methods to Predict the Immunogenicity of Therapeutic Coagulation Proteins

September 17-18, 2015
Ruth Kirschstein Auditorium, Natcher Building, NIH Campus, Bethesda MD

SPONSORS

FDA
NIH National Heart, Lung, and Blood Institute
PPTA
National Hemophilia Foundation for all bleeding disorders
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Glenn Pierce, World Federation of Hemophilia
Mike Soucie, Centers for Disease Control and Prevention
Johannes Oldenburg, University of Bonn
Miguel Escobar, University of Texas
Alessandro Sette, La Jolla Institute for Allergy & Immunology
### The stakeholders in the inhibitor problem

**Patient ● Caregiver ● Healthcare system**

- Economic and human costs
- Safety and efficacy of the drug is compromised
- Interaction with endogenous protein can be life-threatening

**Industry**

- Added risk to the drug development cost
- Attrition
- Lack of predictive tools means ADAs detected only in late phase 3 trials after significant expenses have accrued

**Regulatory agencies**

- Bioengineered products are becoming the norm
- Immune consequences of neo-epitopes difficult to evaluate
- In small trials patients may not represent full genetic diversity of proteins involved in immune response
Why this workshop? Why now?

**New Advances**
In immunology, bioinformatics & computational biology
Growing interest on the part of industry to use predictive tools for immunogenicity

**New initiatives**
My Life, Our Future: Genotyping for Progress in Hemophilia (NHF)
ABIRISK - Anti-Biopharmaceutical Immunization prediction and analysis of clinical relevance to minimize the **RISK** (European Innovative Medicines Initiative)

**New concerns**
Novel engineered coagulation proteins are emerging from the drug development pipeline
Greater risks identified for subsets of patients
## Workshop Scope

<table>
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<th>Topic</th>
<th>Details</th>
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| **Mapping the landscape**                  | The genetic determinants of immunogenicity  
The importance of well characterized clinical samples – Planning for success now and in the future  
Glycobiology and immunogenicity             |
| **The resources**                          | Registries and data-bases  
Genotyping initiatives and biological samples  
Sharing resources  
PUPs!!!                                         |
| **Genetic information**                    | The transition from hypothesis driven studies of individual genes to wider genomic studies                                               |
| **Bioengineered products: Lessons learned**| Experience has been largely positive  
The FVIIa analog experience: Novo Nordisk & Bayer                                                                                  |
| **Validating existing and emerging technologies** | IMI and ABIRISK  
The future—integrating data for better patient outcomes  
The challenge of de-immunization          |
| **Once inhibitors occur**                  | New strategies for ITI  
Markers for early intervention                                                             |
New & disruptive technologies- how industry and regulatory agencies respond will determine how much patients benefit

- The ability to inexpensively generate *and* analyze vast amounts of genetic data is poised to foster a wave of disruptive technologies
- Protein engineering, vector based gene therapy, and iPSC/transgene combinations offer unique scientific approaches toward disease management/cure
- Assessing safety- Regulatory pathways
- Assessing safety- Patient evaluation short and long term
- Assessing efficacy- Short term and duration
Genetic Determinants of Immunogenicity Panel
Gouw/Oldenburg Panel discussion

• How much do we know about FVIII genotype and inhibitor development and what are the additional work to be done?
• What are the other genetic determinants of immunogenicity: current status and future directions?
• How to interpret these findings in new hemostatic agents?
• “Hypothesis driven” vs. “hypothesis free” studies to identify genetic determinants of immunogenicity; pros and cons.
• How can the community gather high quality information?
• Should preclinical genetic studies be used to inform clinical trials?
  • For example the identification of potentially high risk HLA alleles for an engineered therapeutic-protein?
  • For potential later guidance of studies when more knowledge is assembled rather than using information now for decision making.

Asking for inhibitor prediction in a given individual is a distant hope. But asking testable hypothesis driven questions in patients at risk is not
Although the Eprex case is most serious, virtually all biotechnology drugs provoke immune response in some patients, though usually just tiny fractions. The reactions are becoming of greater concern as the number of protein drugs increases.

Company Announcement

28 September 2012

Novo Nordisk discontinues development of vatreptacog alfa following analysis of phase 3 results

Novo Nordisk today announced the decision to discontinue the development of vatreptacog alfa, a fast-acting recombinant factor VIII analogue for haemophilia patients with inhibitors. The decision follows analysis of the data from the phase 3a trial adept™2. On 9 August, Novo Nordisk announced that a few patients in the trial had developed anti-drug antibodies to vatreptacog alfa, one patient with a potentially neutralising effect.
PUP Panel

1. Are PUPs more useful in understanding the scientific basis of immunogenicity or making comparative determinations of immunogenicity of alternative products?

2. Is PUP data needed to demonstrate safety of a new molecule?

3. What approaches should we take to study immunogenicity in PUPs in the future?

4. Are there key scientific questions that could benefit from studies in PUPs?

5. Potential for clinical/academic/industry sponsor collaborations. Do regulatory agencies and/or NIH have a role? Roles of international registries?

Current PUP EMA regulatory requirements and BioPharma’s lack of urgency are hindering the search for solutions to inhibitors.
Significant time has been spent analyzing product specific inhibitor risk in PUPs

A lot of PUPs have been used to ascertain a primary endpoint of inhibitor development

Data are contradictory and less useful (sensitive) than PTP data when looking for immunogenicity

Two modified FVIIa’s have proven this PTP point recently

Isn’t it time to utilize this precious resource to test hypotheses to prevent and treat inhibitors?
REQUEST FOR PROPOSALS

Clinical Trials of Immune Tolerance for Protein/Gene-Replacement Therapy

The Immune Tolerance Network (ITN) is an international clinical research consortium founded by the National Institute of Allergy and Infectious Disease of the National Institutes of Health, with the mission to accelerate the clinical development of immune tolerance therapies through a unique collaborative. The ITN is currently inviting proposals for novel clinical trials with the aim of inducing tolerance in patients who receive gene/protein-replacement (e.g. hemophilia, Gaucher’s disease) or other exogenous protein therapy, in which the patients are at risk for developing an immune response to the biologic agent. The ideal proposal would meet the following criteria:
Immune Tolerance Network RFPs

1. The therapeutic strategy should include an antigen or modified antigen and have the potential to be used with an additional immunomodulatory agent(s);

2. The proposal should be supported by strong rationale or preclinical data that supports a testable mechanism of action for tolerance induction;

3. There must be an appropriate patient population suitable for enrollment with an opportunity to significantly advance clinical practice; and with a plan for risk mitigation in the study design;

4. Information is available regarding the molecular details of immune recognition (e.g. T cell epitopes, MHC restriction, B cell epitopes);

Please direct all proposal submissions and any questions concerning this RFP to:

Philip Bernstein, PhD
Executive Director of Strategic Review and Planning
Tel: (240) 235-6132
Email: pbernstein@immunetolerance.org

Consider combination B- and T-cell therapies with preservation of Tregs-more aggressive approach
The Unknown
by Donald H. Rumsfeld

As we know,
There are known knowns.
There are things we know we know.
We also know
There are known unknowns.
That is to say
We know there are some things
We do not know.
But there are also unknown unknowns,
The ones we don't know
We don't know.

THANK YOU