Meeting Report

2012 AAPS National Biotech Conference Open Forum: A Perspective on the Current State of Immunogenicity Prediction and Risk Management

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Abstract. The immunogenicity profile of a biotherapeutic is determined by multiple product-, process- or manufacturing-, patient- and treatment-related factors and the bioanalytical methodology used to monitor for immunogenicity. This creates a complex situation that limits direct correlation of individual factors to observed immunogenicity rates. Therefore, mechanistic understanding of how these factors individually or in concert could influence the overall incidence and clinical risk of immunogenicity is crucial to provide the best benefit/risk profile for a given biotherapeutic in a given indication and to inform risk mitigation strategies. Advances in the field of immunogenicity have included development of best practices for monitoring anti-drug antibody development, categorization of risk factors contributing to immunogenicity, development of predictive tools, and development of effective strategies for risk management and mitigation. Thus, the opportunity to ask "where we are now and where we would like to go from here?" was the main driver for organizing an Open Forum on Improving Immunogenicity Risk Prediction and Management, conducted at the 2012 American Association of Pharmaceutical Scientists' (AAPS) National Biotechnology Conference in San Diego. The main objectives of the Forum include the following: to understand the nature of immunogenicity risk factors, to identify analytical tools used and animal models and management strategies needed to improve their predictive value, and finally to identify collaboration opportunities to improve the reliability of risk prediction, mitigation, and management. This meeting report provides the Forum participant's and author's perspectives on the barriers to advancing this field and recommendations for overcoming these barriers through collaborative efforts.

KEY WORDS: ADA; anti-drug antibodies; immunogenicity; neutralizing antibodies; prediction; predictive sciences; risk assessment; risk management; risk mitigation.

INTRODUCTION

Over the past three decades, a diversity of biotherapeutic modalities, from recombinant proteins to monoclonal antibodies and their various derivatives have evolved along with increasingly efficient production and improved quality. Despite these strides, biotherapeutics continue to induce the "side-effect" of "unwanted immunogenicity," defined as an immune response to the biotherapeutic itself. Besides the clinical consequences to safety and efficacy, immunogenicity can have a significant impact on project timelines, development costs, and the regulatory approval process. The successful implementation of well-devised risk assessment and mitigation plans, resulting in significant improvement of benefit/risk profiles for promising biotherapeutics, has resulted in renewed efforts to improve prediction and mitigation of immunogenicity (1–3).

The American Association of Pharmaceutical Scientists' (AAPS) National Biotechnology Conference Open Forum on "Improving Immunogenicity Risk Prediction and Management" (24th May 2012, San Diego, CA), organized by Drs. Bonita Rup (Pfizer) and Meena Subramanyam (Biogen Idec), aimed to discuss the salient risk factors for predicting immunogenicity, reliability of tools currently available for predicting immunogenicity, as well as strategies that have been adopted by the industry for the management of immunogenicity of biotherapeutics.

The Open Forum was divided into two sessions (Tables I and II), one focused on immunogenicity risk prediction and the other focused on the immunogenicity risk management.

State of the Immunogenicity Problem

Dr. Gopi Shankar (Janssen R&D) helped set the stage by providing an overview of the continuing concerns of immunogenicity and introduced important questions that are being addressed in the field, such as:

- What is a clinically meaningful threshold of immunogenicity? What is a significant incidence, titer, or kinetics of ADA?
- How can we start dissecting the interlinked product and patient attributes that lead to induction of immunogenicity?

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Table I. Morning Session

Speaker name	Title of the presentation	Organizational affiliation	AAPS affiliation
Dr. Gopi Shankar	State of the Immunogenicity Problem	Janssen R&D	TPIFG Chair
Dr. Susan Kirshner	Immunogenicity Risk and Management from Regulatory Perspective	FDA	TPIFG Ad Hoc Steering Committee Member
Dr. Bonnie. Rup	Biotherapeutic Immunogenicity Risk Factors, the Science, Reliability and Concepts or Implementing Predictive Tools	Pfizer	TPIFG Past Chair, Immunogenicity Prediction Action Program Area Sponsor
Dr. Manoj Rajadhyaksha	Results of Survey on the Use of Predictive Tools and Gaps	Regeneron Pharmaceuticals, Inc	AAPS Therapeutic Protein Immunogenicity Steering Committee Member and Predictive Immunogenicity Action Program Area Sponsor
Dr. George Gunn	Foreign Sequences	Janssen R&D	TPIFG Member
Dr. Alyssa Morimoto	Pre-existing Antibodies	Roche	TPIFG Member
Dr. Harald Kropshofer	Aggregates/Formulation and Route of Administration	(Genentech, Inc) Roche	TPIFG Member

- Can we develop reliable *in silico*, *in vitro*, *ex vivo*, or *in vivo* tools that would predict clinical outcomes of immunogenicity?
- Can we establish tolerizing regimens for various biotherapeutic modalities?

To address these and similar questions, the AAPS Therapeutic Protein Immunogenicity Focus Group (TPIFG) established several Action Program Areas (APAs): Uniform Reporting of Immunogenicity, Immunogenicity Prediction (IPAPA), and Immunogenicity Mitigation. More information on each of these APAs is available at the TPIFG website http://www.aaps.org/Therapeutic_Protein_Immunogenicity/

Survey on the Use of Predictive Tools

Dr. Manoj Rajadhyaksha (Regeneron Pharmaceuticals Inc.) provided a synopsis of “Where we are” based on responses to the Predictive Immunogenicity Survey conducted by the TPIFG-IPAPA. Some key observations from the survey that he described were:

- Fifty percent of the respondents already employed methods of immunogenicity prediction to minimize immunogenicity as well as for candidate selection.
- More than 80% of respondents wanted to hear more about regulatory authorities' positions with respect to utility of predictive tools.

- Some notable gaps identified were:
 - Lack of standardization of the methods/tools, proof of concept, and limited clinical correlation of the prediction data (Fig. 1).

Regulatory Authority Perspective

Dr. Susan Kirshner (FDA) emphasized that predictive tools can improve the accuracy of risk assessments and inform risk mitigation. Where necessary the agency does request predictive data. Some key messages from her presentation were:

- Assay tools that evaluate the T, B, or antigen presenting cell compartments could be applied not only to lead candidate selection but could also add value during clinical trial stages, where applicable.
- Mitigation plans should include strategies to manage safety events quickly and effectively. Some suggested strategies were consideration for longer observation periods before dosing additional patients, trial stopping rules, and monitoring of ADA in real time when necessary.
- With realization that clinical trial time frames and population size are limited, postmarketing surveillance

Table II. Afternoon Session

Speaker name	Title of the presentation	Organizational affiliation	AAPS affiliation
Dr. Meena Subramanyam	The Transition from Immunogenicity Risk Assessment to Risk Management: A Historical Perspective on Managing Immunogenicity Risk over Multiple Decades of Biotherapeutic Use	Biogen Idec, Inc.	TPIFG Steering Committee member
Dr. Jaya Goyal	Common Assay Initiative for Interferon Beta	Biogen Idec, Inc.	TPIFG Member
Dr. Edward Gomperts	Hemophilia: its therapy and the comprehensive response to the development of inhibitory antibodies	Saban Research Institute	Invited Guest Speaker
Dr. Susan Richards	Ligand Binding Assay Bioanalytical Focus Group	Genzyme Corp.	TPIFG Chair-Elect
Dr. Sofie Pattijn	Overview of European Immunogenicity Platform	Lonza	EIP Member

Fig. 1. Gaps or barriers towards broader implementation of predictive immunogenicity. Illustrates the responses obtained during the Predictive Immunogenicity Survey on the question, “What do you see as the gaps or barriers to broader implementation of predictive immunogenicity screening at present?” Lack of proof of concept, benchmarking studies, and lack of clinical correlation with available predictive tools were the main issues highlighted by these responses. This has particularly stemmed from very little data and lack of case studies in the public domain. Such a situation prevents clear assessments of the utility of these tools and does not provide an opportunity to investigate whether these tools need to be further improved in their sensitivity and specificity for clinical correlation

(to ascertain the prevalence and impact of immunogenicity in the wider population) is gaining importance. This aspect has already demonstrated value in effectively managing patients on enzyme replacement and multiple sclerosis therapies. Two approaches suggested by Dr. Kirshner were:

- Global consortiums to manage resource-intensive phase IV studies which provide opportunity for meta-analysis of data.
- Direct reporting by physician or patient to FDA through internet-based frameworks.

Biotherapeutic Immunogenicity Risk Factors, the Science, Reliability, and Concepts on Implementing Predictive Tools

Dr. Bonnie Rup (Pfizer) provided an Industry Perspective on advancing predictive immunogenicity science. The lack of data correlating predictive tools and clinical outcome is a gap that has led to lack of confidence in the available tools. Cross industry and academia collaborations operating in a noncompeting manner bringing forth case studies to generate industry standards and guidances could be a potential solution to address some of these observed gaps. The Innovative Medicines Initiative ABIRISK consortium and the TPIFG-IPAPA were cited as two ongoing cross-industry collaborative efforts intended to characterize risk factors and advance immunogenicity prediction science.

Recommendations for Improving Risk Prediction

The TPIFG-IPAPA has formed subteams for further understanding of specific risk factors (pre-existing

ADA, subcutaneous (SC) administration, foreign sequences, formulation, and aggregation). Breakout sessions to discuss recommendations of those subteams were moderated by Dr. Li Xue, (Pfizer), Dr. Renuka Pillutla, (Bristol Myers Squibb), Dr. Leslie Cousens (Epivax), and Dr. Valerie Quarmby (Genentech) and provided the following recommendations and action items:

1. Lack of understanding about immunogenicity risk potential of these factors was attributed to insufficient data in the public domain. This observation was made in the predictive immunogenicity survey as well as the pre-existing antibody survey (Fig. 2). Therefore, a systematic collection of data and analysis, through sharing case studies and data, was recommended.
2. Publishing the pre-existing antibodies survey results was recommended to raise the awareness of this risk factor and its impact in context of different patient populations.
3. There is a need to establish if SC is a consistent risk factor that should be considered in isolation or in context of other known risk factors. Literature searches, surveys, and review of academic research in animals could suggest mechanistic causes for further investigation. There was unanimous support and great interest to recommend industry-wide collaborative efforts that could conduct a deep dive analysis towards understanding SC and other routes of administration as risk factors of immunogenicity.
4. Mechanisms should be devised for sharing data in a noncompeting manner that would be acceptable to industry sponsors, including legal and regulatory departments.

Fig. 2. Gaps in understanding pre-existing antibodies. Illustrates some of the responses that were obtained during the “Preexisting antibodies as a risk factor for immunogenicity” Survey. This figure graphically shows the responses to the question, “What are the current gaps or barriers towards understanding pre-existing antibodies”. These responses showed that lack of understanding of pre-ADA as a risk factor, lack of regulatory guidance, and lack of benchmarking studies to demonstrate clearly pre-ADA as a risk factor, were the key concerns that needed to be resolved. The Open Forum recommendations of compiling studies and data that can better evaluate pre-existing ADA as a risk factor have been put into action by the IPAPA subteam on “pre-existing antibodies”

Immunogenicity Risk Management

Dr. Meena Subramanyam (Biogen Idec) provided an overview of some key concepts around immunogenicity risk management, including the successful use of global consortiums and registries. Some of her key messages were:

- A comprehensive risk management plan (RMP) should be designed to identify, assess, communicate, and minimize risk throughout the life cycle of a drug to demonstrate a favorable benefit-risk profile in patients
- A RMP should inform physicians of the known frequency of ADA incidence and associated clinical effects. One example of a global consortium was The Prospective Immunogenicity Surveillance Registry setup for monitoring of EPO-mediated PRCA reactions in dialysis patients. This was conducted through global participation of patients who underwent extended monitoring period of 3 years post-enrollment (1). Data collection via questionnaire and access to validated anti-EPO ADA assay along with a case adjudication committee were some of the associated strategies that were employed in this effort.
 - Securing an agreement with regulators on the “Gold Standard” assay for ADA detection, making it readily accessible to physicians through accredited CLIA labs, developing a product-specific guidance document on interpretation of immunogenicity data in context of clinical effects are some key attributes of a well-designed RMP.
 - Towards providing an example of a Gold Standard assay, Dr. Subramanyam described the development of a standardized global assay for monitoring the

immunogenicity of products to treat hemophilia A led by the National Heart, Lung, and Blood Institute Working Group. The working group developed a list of characteristics for the assay, notably:

It should be validatable within the established reference ranges, able to detect and characterize phenotypic variability in the manufactured products (native plasma-derived and bioengineered products) and demonstrate clinical utility and predictive power for diagnostic and therapeutic monitoring across a broad hemostatic range in various diseased populations.

Further focusing on this topic, Dr. Jaya Goyal (Biogen Idec) described “Development and validation of a common assay for the detection of anti-drug neutralizing antibodies to Interferon beta products” that was initiated at the request of the EMA. A cross-industry/academia collaboration was established between Biogen Idec, Serono, and Berlex Laboratories and coordinated by Dr. Huub Schellekens (Utrecht University). Dr. Edward Gomperts, a practicing physician in hemophilia indication shared his experience of the significant advances made in hemophilia treatment through multiple collaborative efforts involving government, consumer, health care, scientific, and manufacturers. Ongoing collaborative efforts related to predicting and mitigating immunogenicity risk include a hemophilia inhibitor genomics study, prophylactic treatment study and an international study on immune tolerance induction.

The forum ended with presentations given by Dr. Susan Richards (Genzyme/Sanofi) and Dr. Sofie Pattijn (Lonza), providing additional examples of successful interest groups working in the immunogenicity management area such as the AAPS-Ligand Binding Assay Focus Group & the European Immunogenicity platform.

Discussion/Recommendations

The Open Forum was a lively and interactive discussion of real and perceived gaps in immunogenicity risk prediction and management in which the attendees agreed that considerable uncertainty remains about the reliability of the risk factors and optimal methods for integration of *in silico*, *in vitro*, and *in vivo* predictive tools in routine drug development process. The stage was set for determining areas in which industry-wide collaboration may help reduce these areas of uncertainty and also identify and address perceived barriers to collaboration. In the predictive immunogenicity area, some of the perceived barriers that were voiced are legal restrictions and competitive disadvantage to sharing information, concerns that different formats for tools being used render data sharing uninformative and lack of clinical data validating the predictive tools. Similar concerns had been expressed in the past regarding validity of ADA and neutralizing antibodies (NABs) measurements considering that clinical correlation with ADA and NAB reactivities is not always observed. However, through collaborative efforts, industry leaders were able to establish common practices for assessing immunogenicity risks and validating ADA and NAB assays. Therefore, the perceived concerns expressed about predictive

immunogenicity should not impede us from moving forward through collaborative opportunities. Some proposed examples of such collaborations are: providing recommendations for validation of the predictive tools, specifications for types of controls to be used, sharing information about analytical performance, determining what sorts of values are meaningful, and constructing recommendations for conducting studies of “cross-correlation” between tools. Specifically, recommendations could be made about comparative studies of (a) *in silico* vs. *in vitro* HLA binding vs. DC-MS tools, (b) ADA incidence vs. *ex vivo* human T cell recall responses, (c) route of administration risk in animal models vs. corresponding human immunogenicity outcomes, and (d) whether the cumulative effect of more than one risk factor improves the clinical correlation as compared with looking at risk factors in isolation. We believe that widespread implementation of these recommendations could open new opportunities for mitigating immunogenicity risk leading to higher rewards in drug development processes.

It is equally important to remember that even highly sophisticated predictive strategies and clinical trial data alone do not provide certainty about the risk involved in the wider population. Therefore, predictive tools cannot be substitutes for a well-designed risk management plan which needs to be in place. Based on the success of collaborative efforts in risk management for Interferon and Factor VIII, it can be anticipated that collaborative efforts spanning academia and industry can establish sound predictive and risk management strategies involving all stake-holders from sponsors (manufacturers) to practicing physicians and including patients.

The Open Forum recommended the following potential solutions against perceived barriers:

- An independent group leading a collaborative effort with masked data that protects proprietary information largely alleviates the concern of intellectual property and facilitates sharing of information.
- A US government sponsored mechanism to address some of these gaps could utilize the Public Private Critical Path (C-Path) Initiative which requests proposals towards “evaluating the predictive value of *ex vivo*, *in vitro*, and computational

methods” and “a comprehensive analysis of immunogenicity data and its relationship to safety and efficacy parameters across multiple products requiring significant collaborations between an industry-consortium, academia, analytical and computational service providers and regulatory agencies in a non-competitive environment.”

- The AAPS TPIFG group through its APAs, with industry, academia, and regulatory membership could identify noncompeting mechanisms of collaborating and providing recommendations. The TPIFG under the auspice of the IPAPA has set up subteams that are already investigating risk factors.
- Collaboration channels established between societies such as AAPS TPIFG and the European Immunogenicity Platform (EIP), can further integrate knowledge and help build consensus across industries on a global scale.

CONCLUSIONS

Concluding from the dialog held at the Open Forum, there remains uncertainty in the reliability of risk factors and predictive tools, which affects development of risk management strategies. Gaps and perceived barriers were identified that have contributed to the current state. Potential solutions and recommendations were provided for consideration by industry, academia, and regulatory authorities.

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