Harmonization of Clinical Immunogenicity Reporting

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Janssen Research & Development, LLC
Biologics Clinical Pharmacology / Biotechnology Center of Excellence

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Harmonization of Clinical Immunogenicity Reporting

An Initiative of the Therapeutic Protein Immunogenicity Focus Group (TPIFG) of the American Association Pharmaceutical Scientists (AAPS)

aaps

Uniform Reporting of Immunogenicity Committee:

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- Arno Kromminga, Ph.D. (*European Immunogenicity Platform*)
- Steven Arkin, MD (*Pfizer*)
- Meena Subramanyam, Ph.D. (*Biogen-Idec*)
- Laurent Cocea, MD, Ph.D. (*Health Canada, CERB/Clinical Evaluation Division*)
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- Susan Kirshner, Ph.D. (*FDA, CDER/Office of Therapeutic Proteins*)
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Harmonization of Clinical Immunogenicity Reporting

The *Uniform Reporting of Immunogenicity* Committee

***Our Goal*:**
To develop a harmonized approach to immunogenicity data interpretation and presentation. We plan to develop global recommendations on the aspects of product immunogenicity that can comprise decision-making criteria for sponsors, health authorities, physicians, and patients.

***Work in progress*:**

• Standardized terminology and definitions - clinically meaningful characteristics of immunogenicity and standardized descriptions of those characteristics

• Recommended sampling schema (for typical dosing schedules) that can help gain necessary information on the aspects of immunogenicity.

• Therapeutic-class, product risk-level, and/or drug development phase based considerations for data reporting

My objective today

- Briefly review the need for harmonized approaches
- What information can assist doctors in determining treatment options? *Results of a survey conducted by AAPS*
- Draft definitions of common terms applied to describe immunogenicity
- Draft approaches to presenting results in an objective manner
- Gather your feedback

Previously at the 3rd EIP symposium…

- Presentation titled "*A Call For Harmonizing Approaches To Clinical Immunogenicity Data Analyses And Presentations*"
- What was available:
  - Regulatory agency (FDA, EMA) guidance documents and some publications by their representatives
  - Several AAPS Whitepapers
- Gap analysis:
  - Inconsistent use of terms (definitions)
  - Inconsistent analysis/presentation of results
  - Information not particularly useful to healthcare professionals
- An AAPS Survey on Immunogenicity *for Physicians only*

Terms used to describe immunogenicity

- **Antibody Incidence**
  - "…only based on higher titer results because the assay lacked sensitivity"
  - "…treatment emergent binding antibodies"
  - "…treatment induced antibodies…"

- **Magnitude (ADA levels)**

  "low titer" versus "high titer" antibodies

  "…equivocal titers"

  "…protocol specified high-titer"

  "…weakly positive"… "…low binding…"

  "…indeterminate" (low signal response)

- **Kinetics / Temporal Patterns**
  - Onset of ADA
    - "…median time to antibody formation"
    - "…median time to peak titer"
    - Early versus late onset
  - Duration of ADA
    - "short-lived"
    - "…transient"
    - "…persistent"
    - "…plateaued"
    - "…downward trend"

Hence the *Call for Harmonization* by AAPS-TPIFG in 2010

- Standard definitions are needed for the descriptors of immunogenicity
- Data presentation in a more useful and objective manner is needed to describe the onset and duration of ADA
- Titer reporting as “high” or “low” *per se* is meaningless and confusing. We must find ways to partition product-specific clinically consequential titer thresholds.
- Kinetics/temporal pattern reporting as “early or late onset” and “transient or persistent ADA response” is confusing due to subjectivity in the definitions applied in publications and product labels. We must develop a common understanding based on objectivity and clinically useful criteria.
- It is important to provide relevant information to clinicians in a concise and consistent manner in product labels. We must make our best attempts to develop product-class specific standards/approaches for reporting immunogenicity

What are doctors interested in knowing?

The AAPS-TPIFG Physician Survey completed in 2011

Demographic Information (N = 49)

Affiliation:

Industry	28
Academia	7
Hospital	4
Private clinic/community practice	8
Governmental Agency	0
Other	1

Types of Patients treated:

Autoimmune disease	32
Cancer	4
Metabolic disease; Enzyme or Fact ...	4
Infectious disease	3
Transplant	5
Other	10

Specialty:

Dermatology	2
Endocrinology	2
Gastroenterology	6
Hematology	0
Immunology	4
Infectious diseases	2
Internal medicine	5
Neurology	3
Oncology	0
Pediatrics	2
Primary care	0
Rheumatology	14
Surgery	1
Other	6

Prescription Experience:

therapeutic antibody	44
fusion protein	27
replacement enzyme	7
pegylated protein	26
Conjugated protein	5
Other therapeutic proteins	10
non-protein therapeutic	1

What are doctors interested in knowing?

Results (Highlights) of the AAPS-TPIFG Physician Survey

(1) PRODUCT LABEL INFO: Information pertaining to immunogenicity in drug package inserts or product labels is _____useful for me to treat my patients safely and effectively

Always: **27 (55%)** **Sometimes:** **20 (41%)** **Never:** **2 (4%)**

(2) CONCERN ON IMMUNOGENICITY: I have _____ concerns about my patients developing ADA following treatment with biologic drugs:

Strong: **10 (21%)** **Moderate:** **26 (54%)** **Limited:** **12 (25%)**

What are doctors interested in knowing?

Results (Highlights) of the AAPS-TPIFG Physician Survey

(3) APPLYING THE INFO: I _____ use immunogenicity information as a factor when choosing treatment options for my patients:

Always: **14 (30%)** **Sometimes:** **27 (59%)** **Never:** **5 (11%)**

(4) APPLYING THE INFO: I _____ compare the immunogenicity rates of biologic drugs when determining treatment options for my patients:

Always: **16 (35%)** **Sometimes:** **22 (48%)** **Never:** **8 (17%)**

What are doctors interested in knowing?

Results (Highlights) of the AAPS-TPIFG Physician Survey

(5) INFO DESIRED: In addition to the incidence (rate) of antibody formation in clinical studies, I would find it useful to learn about:

Presence of pre-existing antibodies before first exposure to the biologic drug	**59%**	ADA magnitude	**74%**
		Impact of NAbs	**90%**
The effect of concomitant immunomodulatory drugs on ADA development	**67%**	ADA isotypes	**41%**
Relationship between drug dose or frequency of dosing and ADA development	**82%**	None of the above	**2%**

What are doctors interested in knowing?

Results (Highlights) of the AAPS-TPIFG Physician Survey

(6) INFO DESIRED: Why? (I am interested in such information because _____):

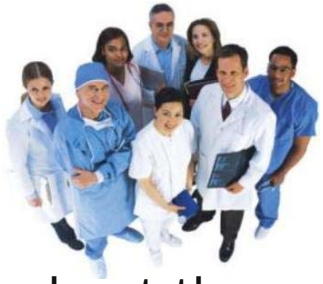
It can help me treat my patients	**29 (59%)**
It is a scientific interest for me	**8 (37%)**
No, this is not useful to me	**2 (4%)**

(7) INFO DESIRED: It is important for me to know whether there might be a clinical impact (safety and/or efficacy) when a patient develops:

Neutralizing antibodies	**8 (16%)**	Both	**41 (84%)**
Non-neutralizing antibodies	**0 (0%)**	Neither	**0 (0%)**

What are doctors interested in knowing?

Results (Highlights) of the AAPS-TPIFG Physician Survey

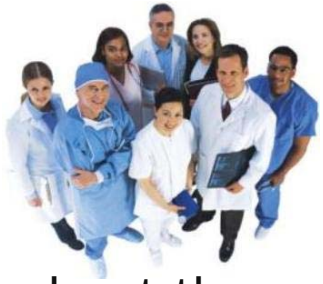


(8) INFO DESIRED: It is useful for me to know the following about the timing of the anti-drug immune response:

When at the earliest after beginning treatment with a biologic could my patient begin to develop ADAs	**39 (80%)**
Whether the ADA diminishes over time	**39 (80%)**
When the ADA is eliminated, and under what conditions (discontinue drug, concomitant immune suppressive therapy, etc)	**35 (71%)**
No, this is not useful to me	**3 (6%)**

What are doctors interested in knowing?

Results (Highlights) of the AAPS-TPIFG Physician Survey



(9) INFO DESIRED: It is useful for me to know the following about the timing of the anti-drug immune response:

When at the earliest, after beginning treatment with a biologic, could my patient begin to develop ADAs ("ONSET")	**39 (80%)**
Whether the ADA diminishes over time ("DURATION")	**39 (80%)**
When the ADA is eliminated, and under what conditions (discontinue drug, concomitant immune suppressive therapy, etc) "DURATION")	**35 (71%)**
No, this is not useful to me	**3 (6%)**

What are doctors interested in knowing?

Results (Highlights) of the AAPS-TPIFG Physician Survey

(10) OPINION: Physicians' perspective on the most important aspects of clinical immunogenicity:

Severe hypersensitivity (anaphylaxis)	**86%**
Reduction or loss of efficacy	**83%**
Drug neutralizing activity	**79%**
Non-severe hypersensitivity (Infusion/injection reactions, rash)	**71%**

And <70% votes for:

- Impact on PK (69%)
- Immune complex disease (62%)
- Autoimmune deficiency (58%)
- Cytokine release syndrome (50%)
- impact on fetal development (47%)

What are doctors interested in knowing?

Results (Highlights) of the AAPS-TPIFG Physician Survey

SURVEY CONCLUSIONS:

- There is clinical need to relate ADA with clinical impact.
- This necessitates descriptive categorization of relevant aspects of ADA immune responses that could be partitioned to elucidate clinically relevant thresholds of incidence (including pre-existing antibodies), magnitude (titer), and kinetics/temporal patterns of ADA.
- Descriptive categorization should be objective as far as possible, but certainly standardized so as to avoid confusions.
- The survey results were not surprising….
We immunogenicity scientists weren't clueless after all!

Work in progress of the AAPS-TPIFG "Uniform Reporting of Immunogenicity" Committee

TACTICAL PLAN:

- Standardize definitions for the descriptors of ADA immune response based on objectivity and clinically useful criteria.

  Draft completed

- Offer data presentation options in a more useful and objective manner to describe the kinetics/temporal patterns of ADA

  Almost there…

- Attempt to develop product-class and risk-level specific standards/approaches for reporting immunogenicity

  Haven't begun

Terms & Definitions - *draft*

- **Simple terminology requiring clarification**:
  - ADA, Binding ADA, Neutralizing ADA, Non-neutralizing ADA, HAMA, HACA, HAHA, Titer.
- **Terms used to describe ADA status of a sample:**
  - **ADA Positive Sample:** when ADA is detected in a sample, the sample is considered positive
  - **ADA Negative Sample:** when ADA is not detected in a sample, the sample is considered negative
  - **ADA Inconclusive Sample:** when ADA is not detected in a sample but drug is present in the same sample at a level that can cause interference in the ADA detection method, then the negative ADA result cannot be incontrovertibly confirmed and the sample should be considered inconclusive. *Whereas the term 'indeterminate' has been also used to describe such a sample it is not advised because it is more commonly used to indicate samples with imprecise analytical results in clinical diagnostic tests*.
  - **Unevaluable Sample:** when a sample could not be tested for ADA due sample loss, mishandling, or errors in sample collection, processing, storage, etc.

Terms & Definitions - *draft*

- **Baseline ADA (pre-existing antibodies):** refers to antibodies reactive with the biologic drug molecule before initiation of treatment.
- **Treatment-induced ADA:** ADA developed *de novo* (seroconversion) following biologic drug administration (i.e., formation of ADA anytime after the initial drug administration *in a subject without pre-existing ADA*).
- **Treatment-boosted ADA**: Pre-existing ADA that were boosted to a higher level following biologic drug administration (i.e., anytime after the initial drug administration the ADA titer is greater by a scientifically reasonable margin, such as a 2-fold or 3-fold).
- **Terms used to describe ADA status of a Subject:**
  - **ADA Positive Subject:** Subject with at least 1 treatment-induced or treatment-boosted ADA positive sample at any time during the treatment or follow-up observation period.
  - **Baseline ADA positive Subject:** An ADA positive subject with baseline positive sample(s), regardless of boosting after biologic drug administration.

Terms & Definitions - *draft*

- **Terms used to describe ADA status of a Subject:**
  - **ADA Negative Subject:** Subject without a treatment- induced or treatment-boosted ADA positive sample during the treatment or follow-up observation period.
  - **ADA Inconclusive Subject:** An ADA non-positive subject who cannot irrefutably be classified as ADA Negative. *To recommend a single definition for this category is not feasible because there can be any of several possible grounds warranting this category for different product classes and disparate circumstances.* Thus, sound scientific rationale incorporating the drug's immunogenicity risk profile, prior experience with the drug, label information or publications on same-class drugs, and/or discussions with regulatory authorities should be considered in developing a fit-for-purpose definition of the ADA Inconclusive subject category. For example:
    - Despite observing some ADA negative samples during a subject's treatment (including follow-up observation period) with a higher risk drug, multiple other samples were found to be inconclusive precluding a definitive conclusion on the ADA status of the subject.
    - Despite all ADA negative samples during a subject's treatment (including follow-up observation period) with a lower risk drug, the last evaluable sample was found to be inconclusive, lending to a conservative ADA inconclusive subject status.

Terms & Definitions - *draft*

- **Terms enabling the reporting of data:**
  - **Evaluable Subjects:** Subjects with at least one sample taken after drug administration during the treatment or follow-up observation period, and is appropriate for ADA testing.
  - **Unevaluable Subjects:** Subjects without a single sample taken after drug administration during the treatment or follow-up observation period, or those who had only unevaluable samples, and therefore cannot be evaluated for immunogenicity.
- **Terms used to describe the characteristics of treatment-induced ADA immune response in a sample set:**
  - **Incidence of ADA (rate of ADA):** refers to the stimulation of a drug-specific ADA immune response, equal to the sum total of treatment-induced and treatment-boosted ADA positive subjects as a proportion of the evaluable subject population. Incidence rates for treatment-induced ADA and treatment-boosted ADA may also be considered separately.
  - **Onset of ADA:** refers to the time period between the initial administration of the biologic drug and the first instance of treatment-induced ADA.
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Terms & Definitions - *draft*

- **Terms used to describe the duration of treatment-induced ADA immune response in a sample set:**

  Transient:

  – Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, as a conservative measure), OR

  – Treatment-induced ADA detected at 2 or more sampling time points during the treatment (including follow-up period, if any), where the first and last ADA positive samples are separated by a period less than 16 weeks , and the subject's last sampling time point is ADA negative.

Terms & Definitions - *draft*

- **Terms used to describe the duration of treatment-induced ADA immune response in a sample set:**

  Persistent:

  – Treatment-induced ADA detected at 2 or more sequential sampling time points during the treatment(including follow-up period, if any), where the first and last ADA positive samples are separated by a period exceeding 16 weeks or longer, OR

  – [By conservative inference] Treatment-induced ADA incidence only in the last sampling time point of the treatment study period, or at a sampling time point with less than 16 weeks before an ADA negative last sample.

  – Additionally, higher risk products may require elucidating the ***off-treatment persistence*** of ADA. In this scenario, it is recommended that subjects be followed up to at least one time point after the last drug administration where both the drug and any transient ADA would be expected to have cleared (a period of time equal to the sum of 5 half lives of the drug (which varies for each drug) *plus* 5 half lives of human ADA (for human IgG1, IgG2, and IgG4 on average, **22 days x 5 half lives = 16 weeks**). ADA detected after the above defined period should be considered persistent off-treatment.

Sampling Recommendations - *draft*

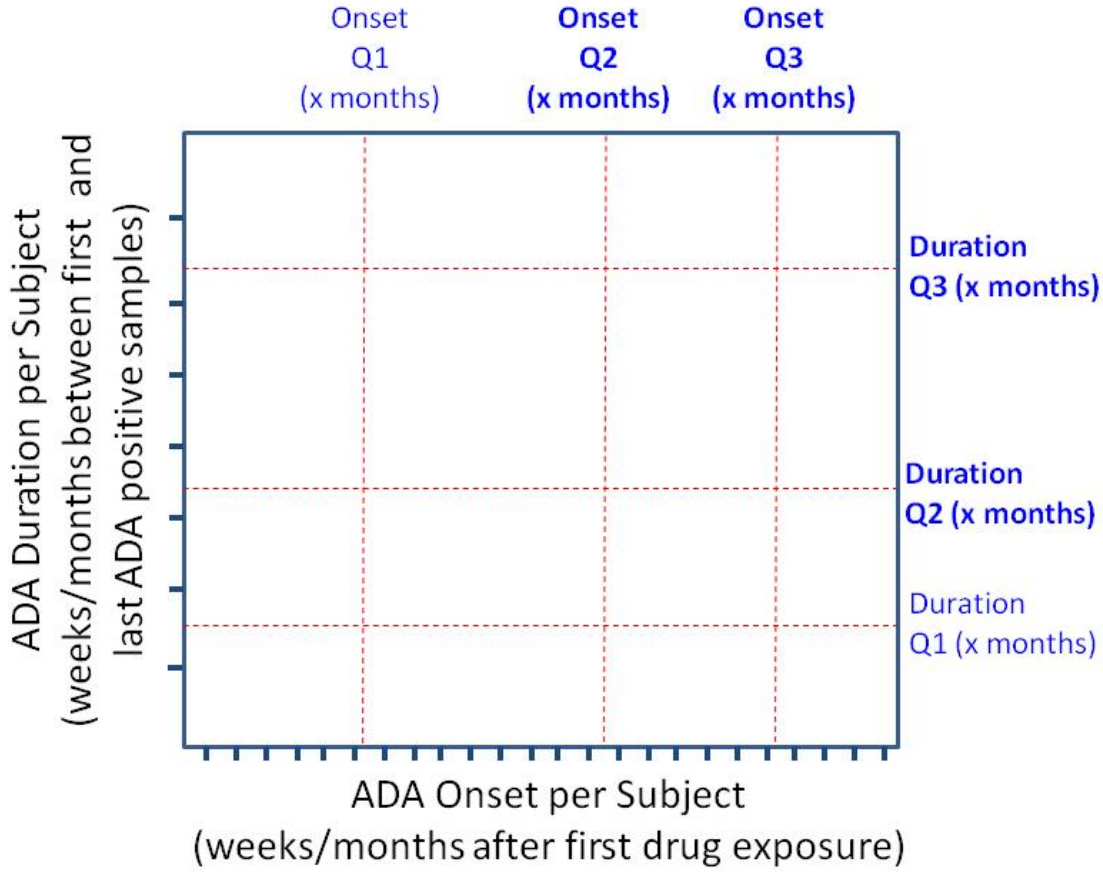
- Sampling frequency during treatment should be designed to maximize the opportunity of detecting treatment-induced ADA and, when applicable, to understand the kinetics.
- At least one immunogenicity sample should be collected following an appropriate period of time after the treatment (i.e., after the last drug administration).
- For the registration (BLA/MAA) of chronic treatments regulatory authorities typically expect immunogenicity data through the first year. Depending on length of the clinical study, collect samples for testing at: 2 weeks, 1 mo, 2mo, 3mo, 6mo, 9mo, 12mo, 18mo, 24mo, and every year thereafter during treatment, and at least one sample collected after an appropriate period of time following the last drug administration (e.g., 16 weeks as recommended earlier).

Descriptive statistics for ADA Kinetics - *draft*

- This approach obviates definitions for ADA immune response kinetics – the onset (early/late) or duration (transient/persistent).
- Applicable only to Treatment-Induced ADA.
- Enables the design of risk management and mitigation strategy because it informs your surveillance schedule.
- *Caveat*: feasible only when sample size is statistically significant. Frequently complex studies with multiple arms and satellite studies may not allow for statistical assessments of immunogenicity.
- For ADA Onset: present the median value (Q2, the "Median time to antibody formation") and the third quartile value (Q3)
  - "When half of the subjects seroconverted" OR "when 75% of the subjects seroconverted"
- For ADA Duration: present the median value (Q2, the "Median time of antibody duration") and the third quartile value (Q3)
  - "The ADAs lasted x months in half of the subjects" OR "The ADAs lasted x months in 75% of the subjects"

Descriptive illustration of ADA Kinetics - *draft*

- A simple graph/plot could provide the reader with an intuitive view of the kinetics of ADA, such as:



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