Detection of Immunogenic Reactions in Clinical Trials of Biosimilars

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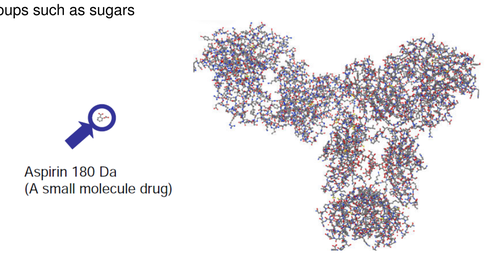
Introduction

Biologics and biosimilars

Biologics

- Biologics (Biological Medical Products, Biopharmaceuticals) are medical products made by living organism, tissues, cells etc.
- Biologics considered in the context of this presentation are **therapeutic proteins** manufactured using a biological expression system. They are:
  - Complex: large molecules ($\approx 1000\times$ the size of a small molecule drug), with complicated folding (3-D structure), and patterns of binding to other chemical groups such as sugars



Complexity of a monoclonal antibody molecule (180,000 Da) versus aspirin
Source: FDA Basics Webinar [1]

  - Sensitive to variations in manufacturing process and handling conditions
    Different manufacturing processes may yield molecules of different structure (even for the same sequence of amino acids)
  - Produced using genetic recombination technology that was pioneered in 1970s.

Biosimilars

- Purported copies of original biologics coming off patents
  - FDA A biological Product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product. [2]
  - EMA A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise. [3]
  - WHO A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product. [4]
- Increasingly important economically as patents of original drugs expire: the estimate for 2015 annual global sales of such drugs is 51 billion US dollars [5]
- Unlikely to be exact copies of original therapeutic proteins because of inherent complexity and sensitivity to details of the manufacturing process. Even for exactly the same sequence of amino acids the molecules would typically show different folding and glycosylation patterns.
- Specific regulatory guidance documents exist for approval of biosimilars (e.g., [2] [3]). **Immunogenicity** (propensity of the therapeutic protein product to generate immune responses to itself and to related proteins or to induce immunologically related adverse clinical events [7]) is a key safety concern for biosimilars.

Immunogenicity

Immune system responses

- Innate (non-specific) immune system reactions include inflammatory reactions. Can be local or systemic. Response immediate.
- Adaptive (acquired) immune system reactions include production of antibodies (humoral B-cells mediated-response) and possibly cellular (T-cells) mediated-response. Response within $\approx$ 1-3 days on the first contact with the antigen, immediate on re-contact.
- Hypersensitivity reactions include allergic reactions and anaphylaxis.

Potential clinical consequences of unwanted immunogenicity

- Loss of efficacy due to binding and/or neutralization of the therapeutic protein by anti-drug antibodies.
- For therapeutic proteins used for substitution, risk of cross-reactivity with the endogenous counterpart.
- Adverse reactions, including serious (anaphylaxis).

Factors influencing immunogenicity of therapeutic proteins

- Protein-related factors: 1) protein size, 2) origin, 3) folding and glycosylation patterns that can hide or expose *T-cell epitopes*, 4) presence of impurities, and 5) formation of aggregates. Assuming the original and biosimilar drugs have the same sequence of amino acids, the difference in immunogenicity will be determined by factors 3–5.
- Genetic factors: allelic polymorphisms and gene defects.
- Patient-related factors: age and previous exposure to similar or related proteins.
- Disease-related factors (chronic infections, impaired immune system, stage of disease).
- Concomitant and previous treatments.
- Duration, route of administration, treatment modalities.

Required immunogenicity assessments

- For biosimilar approval, regulatory agencies require an assessment of immunogenicity in a comparative clinical trail
  (...) at least one clinical study that includes a comparison of the immunogenicity of the proposed product to that of the reference product will be expected. [2]
- Post-marketing assessment of immunogenicity in pharmacovigilance surveillance studies may be also required. [2] [3]

Assessment of immunogenicity Primarily, by development and validation of appropriate assays for the presence and titre of binding antibodies and for neutralizing antibodies [2] [6]. EMA guidance [6] discusses the use of two-stage assays: *screening* and *confirmatory* assays.

Methods and Results

Notation

Consider data from a comparative, parallel group clinical trial of a biosimilar and an innovator (reference) drug. Denote by:

- T_1 and T_2 treatment groups for, respectively, the innovator drug and the biosimilar,
- C_1 and C_2, set of patients, respectively, with and without immunogenic reactions,
- π_1 and π_2 proportions of patients with immunogenic reactions for both arms,
- $p(\mathbf{x}|T_i)$ and $p(\mathbf{x}|C_j)$ probability densities of covariate vector $\mathbf{x}$, respectively, in treatment group T_i and class C_j.

Classification using the Bayes decision rule

Consider loss λ_{ij} associated with classification to class C_i if the real state is C_j.
The Bayes decision rule is to take the action that minimizes the posterior expected loss. It can be shown that the rule requires to:

$$\text{Choose } C_1 \text{ if } \frac{p(\mathbf{x}|C_1)}{p(\mathbf{x}|C_2)} > \frac{\lambda_{12}-\lambda_{22}}{\lambda_{21}-\lambda_{11}} \times \frac{p(C_2)}{p(C_1)}, \text{ otherwise choose } C_2. \quad (1)$$

The decision rule is equivalent to evaluating if the likelihood ratio exceeds a threshold determined by the loss matrix and prior probabilities.
In frequentist interpretation, the ratio $p(C_2)/p(C_1)$ in equation (1) would be, for treatment group i, the ratio $(1-\pi_i)/\pi_i$.

Two-stage classification
Assuming that the loss functions are on a monetary scale, the same rule can be applied to two-stage classification considering both the assay cost and misclassification cost for two sequentially performed assays:

- an inexpensive screening assay, and
- a more expensive and accurate confirmatory assay.

The problem of choosing optimal thresholds in two-stage diagnostic testing was recently considered by Longford [8]; his results are directly applicable to the detection of immunogenic reactions using screening and confirmatory assays.

Mixture model

The probability densities of covariates in both treatment arms are modeled as mixtures of densities from two groups of patients, C_1 and C_2, respectively, with and without immunogenic reactions:

$$\begin{aligned} p(\mathbf{x}|T_1) &= \pi_1\, p(\mathbf{x}|C_1) + (1-\pi_1)\, p(\mathbf{x}|C_2) \\ p(\mathbf{x}|T_2) &= \pi_2\, p(\mathbf{x}|C_1) + (1-\pi_2)\, p(\mathbf{x}|C_2) \end{aligned} \quad (2)$$

The mixing proportions π_1 and π_2 are assumed to be known and different.
The mixture model holds if $p(\mathbf{x}|C_i, T_i) = p(\mathbf{x}|C_i)$.
The probability densities of features in the groups of subject with and without immunogenic reactions can be calculated by inverting mixture equations:

$$\begin{aligned} p(\mathbf{x}|C_1) &= a_{11}\, p(\mathbf{x}|T_1) + a_{12}\, p(\mathbf{x}|T_2) \\ p(\mathbf{x}|C_2) &= a_{21}\, p(\mathbf{x}|T_1) + a_{22}\, p(\mathbf{x}|T_2), \end{aligned} \quad (3)$$

where

$$\begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} \pi_1 & 1-\pi_1 \\ \pi_2 & 1-\pi_2 \end{bmatrix}^{+}$$

(here, $^+$ denotes the Moore-Penrose pseudo-inverse of a matrix.)

Non-parametric classification

The idea is to use non-parametric estimator of densities $p(\mathbf{x}|T_i)$ (e.g., kernel method) within treatment groups then use plug-in estimates to estimate $p(\mathbf{x}|C_i)$ using (3) and finally select class C_i using Bayes decision rule (1).

Statistical properties of the method [9]

- For unbiased estimator of $p(\mathbf{x}|T_i)$, the estimator of $p(\mathbf{x}|C_i)$is also unbiased.
- When the estimator of $p(\mathbf{x}|T_i)$ converges to $p(\mathbf{x}|T_i)$ (with probability one, in probability, or in the mean), the estimator of $p(\mathbf{x}|C_i)$ also converges to $p(\mathbf{x}|C_i)$ in the same mode of stochastic convergence.
- Classification is asymptotically optimal, assuming a consistent estimator of $p(\mathbf{x}|T_i)$.
- It is possible to estimate the misclassification rate, sensitivity, and specificity (or their upper bounds) using methods described previously [9].

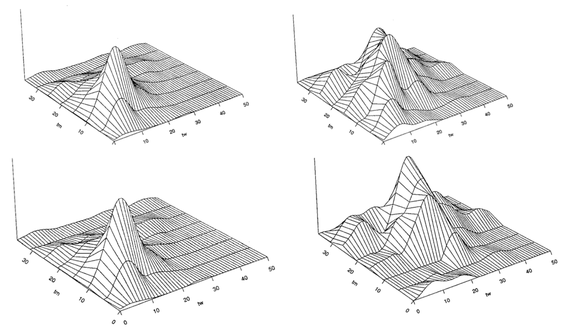


Figure: Example of kernel density estimates by treatment group (top row) and derived class density estimates (bottom row) [9].

Summary and Conclusions

- Biosimilars have a major economic significance.
- Immunogenicity assessment of biosmilars is important for approval of biosimilars: clinical comparison is required by regulatory agencies.
- Optimal Bayes decision rules for detection of immunogenic reactions can be formulated.
- Under mixture model with known mixture (and different) weights an asymptotically optimal detection technique may be used based on inversion of mixture equations.

References

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