Biologic Pharmacovigilance: Key Considerations for Pharmacists

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This webinar is intended to be a primer for Update on Biologics and the Emerging Classifications of Biosimilars, a 2-hour live session on Friday, March 27, 2015, 3:30PM-5:30PM PT, at the APhA Annual Meeting and Exposition.

To register for APhA2015, held March 27-30, 2015, in San Diego, go to aphameeting.org

Other biologics webinars located at pharmacist.com:
The Emerging Role of Biosimilars
Archived webinar from March 4, 2015 broadcast – Coming Soon!
The Emerging Role of Biologics
Archived webinar from March 5, 2015 broadcast – Coming Soon!
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Disclosures

- Steven Lucio, PharmD, BCPS, is an employee of Novation, LLC.
- APBA’s editorial staff declare no conflicts of interests or financial interests in any product or service mentioned in this activity, including grants, employment, gifts, stock holdings, and honoraria. For complete staff disclosures, please see the Education and Accreditation Information section at www.pharmacist.com/education.
Learning Objectives

- Discuss the immunogenic risks and other adverse events associated with biologic medications, both originators and biosimilars
- Review the requirements of the U.S. Food and Drug Administration for effective biosimilar pharmacovigilance
- Describe the European experience with biosimilar monitoring and safety
- Identify the elements of a comprehensive pharmacovigilance program including strategies to support patient education and adherence

Which of the following would be an example of a biologic immune mediated adverse reaction?

- Hypoglycemia due to an excessive dose of insulin
- Antibody development following treatment with infliximab
- TB infection following treatment with infliximab
- Thrombosis in a patient receiving bevacizumab

Which of the following would be the most appropriate for the evaluation of immunogenicity in an epoetin biosimilar?

- Pre-marketing evaluation in chemotherapy patients
- Post-marketing evaluation in chemotherapy patients
- Pre-marketing evaluation in chronic kidney disease patients
- Post-marketing evaluation in chronic kidney disease patients
Which biologic characteristic decreases the risk of immunologic events?

a. Post-translational modifications
b. Subcutaneous administration
c. Intravenous administration
d. Protein folding and aggregation

Pharmacovigilance

- ...is “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”

www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/

WHY DO WE NEED EFFECTIVE PHARMACOVIGILANCE OF BIOSIMILARS BIOLOGICS ALL MEDICATIONS?
Post-Approval Medication Recalls

- Between 1980 and 2009, 740 new molecular entities were approved
- During that time, 26 drugs (3.5% of approvals) were withdrawn primarily due to safety concerns

Do You Remember?

- Astemizole (Hismanal; Janssen)
- Troglitazone (Rezulin; Parke-Davis/Warner Lambert)
- Cisapride (Propulsid; Janssen-Ortho)
- Terfenadine (Seldane; Hoechst Marion Roussel)
- Rapacuronium (Raplon; Organon)
- Cerivastatin (Baycol; Bayer)
- Aprotinin (Trasylol; Bayer)
- Drotrecogin alfa (Xigris; Lilly) – withdrawn due to lack efficacy

Too Recent to Forget?

- Multistate Outbreak of Fungal Meningitis and Other Infections
- www.baxter.com/information/safety_information/heparin_background_information.html
- www.cdc.gov/hai/outbreaks/meningitis.html

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Risk Evaluation and Mitigation Strategies (REMS)

EFFECTIVE PHARMACOVIGILANCE IS ESSENTIAL TO QUALITY CARE

Pharmacovigilance in the Current State

- Drug safety surveillance becoming increasingly complex as it encompasses:
  - Pharmacological properties of medications
  - Use of products in actual practice
  - Product integrity and quality throughout the supply chain
Challenges to Effective Pharmacovigilance

- Low level of reporting
  - Perhaps only 6% of adverse drug events reported
  - Whose responsibility is it to report?
- Quality of reports
  - Increased number of low-quality reports not beneficial
- Inadequate provider education
- Access to timely and accurate information about medication adverse event profiles

Limitations in Pharmacovigilance Data

- Minimal data on indications for use
- Minimal data on product identifiers
  - Cross-sectional study of biopharmaceutical traceability
    - Batch numbers reported 24% of the time for biopharmaceuticals (U.S.)
    - Batch numbers reported 21.1% of the time for biopharmaceuticals (U.K.)
  - Batch number reporting rate 7.4% and 3.6% for U.S. and U.K. small molecules, respectively

PHARMACOVIGILANCE IMPLICATIONS FOR BIOSIMILARS
Biosimilars vs. Generics

- Biologics differ from small molecules
  - Large, complex structures
  - Inherent complexity and variability in manufacturing
  - Greater immunogenicity potential

Biologic Immune Responses

- Large globular proteins that can induce a range of immune responses
- Factors contributing to immunogenicity:
  - Post-translational modifications
  - Higher order structure
  - Aggregation

<table>
<thead>
<tr>
<th>Product</th>
<th>Antibody Formation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>15-52</td>
</tr>
<tr>
<td>Factor IX</td>
<td>1-2</td>
</tr>
<tr>
<td>Interferon α</td>
<td>44</td>
</tr>
<tr>
<td>Interferon β</td>
<td>&lt;5</td>
</tr>
<tr>
<td>II1 Ra</td>
<td>2</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>1-2</td>
</tr>
<tr>
<td>Infliximab</td>
<td>17-60</td>
</tr>
</tbody>
</table>
THE LEGACY OF EPREX

Biologic Pharmacovigilance (Eprex – Example)

- Eprex – Branded version of epoetin alfa marketed in Europe
- Not a biosimilar!
- In 1998, the product was reformulated to remove human serum albumin (due to concerns about variant Creutzfeldt-Jakob disease); replaced with polysorbate 80 and glycine


Biologic Pharmacovigilance (Eprex – Example)

- Pure red cell aplasia (PRCA)
  - Rare anemia syndrome associated with resistance to recombinant human erythropoietin (epoetin) therapy and neutralizing antibodies against erythropoietin

Biologic Pharmacovigilance (Eprex – Example)

- Between 1988 and 1998, three cases reported of patients receiving epoetin developing PRCA
- Between January 1998 and April 2004, 175 cases of PRCA reported in patients on Eprex

Eprex and PRCA

- Definitive cause of PRCA unknown; however, possible contributing factors include:
  - Route of administration (more common with subcutaneous than intravenous injection)
  - Appropriate storage requirements not met
  - Change in formulation
    - Interaction with uncoated rubber plungers
- Corrective measures implemented
  - Limited route of administration to intravenous only
  - Reinforced storage requirements
  - Replaced existing plungers with ones that were coated
- Incidence of PRCA returned to pre-1998 levels

Impact of Eprex PRCA Event

- Elevated the concern about adverse events associated with manufacturing changes of originator biologic drugs
  - And now by extension biosimilars
- As a result, very strict requirements for immunogenicity and safety testing have been set by regulatory authorities
Biologics Price Competition and Innovation Act of 2009

- Gave FDA authority to approve “highly similar” versions of previously approved biologics
- Biosimilars must demonstrate safety, purity and potency
- Biosimilars subject to REMS programs just as reference originator products


Assessment of Immunogenicity

- “…establishing that there are no clinically meaningful differences in immune response between a proposed product and the reference product is a key element in the demonstration of biosimilarity”
- Can be demonstrated through pre- and post-marketing testing


Assessment of Immunogenicity

- Severity and incidence of immune response considered in trial design
- Generally only need to demonstrate that the immunogenicity of the biosimilar is not higher than the reference product

Assessment of Immunogenicity

- Head-to-head study recommended, biosimilar vs. originator
- Recommend evaluating for one year, unless justified
- Study population must also be justified with FDA
  - Most likely to show immune response (e.g. autoimmune vs. malignancy)

The Importance of Clinical Immunogenicity Testing

Clinical Immunogenicity

Clinical Knowledge (e.g., Post-Market Experience)

Human Pharmacokinetics and Pharmacodynamics

Structural and Functional Characterization

Adapted from FDA Webinar: Biosimilar Biological Products

Sandoz Filgrastim Review

- None of the patients in the phase III trial comparing Sandoz filgrastim to the reference product developed anti-drug antibodies
- No clinically meaningful differences between biosimilar and reference product
Tbo-filgrastim Review and Approval

- Product approved as a separately licensed biologic and not a biosimilar
  - However, biosimilar in European Union
- FDA determined that further study of immunogenicity could be done on a post-approval basis

What Can We Learn From Europe?

- Written by members of working committee on biosimilars from EMA
- Reviews seven reasons by which clinicians have expressed concerns in using biosimilars, thus contributing to modest uptake
- The third and fourth reasons relate to immunogenicity and pharmacovigilance, respectively
European Biosimilar Safety: (Filgrastim)

- Review of EMA dossiers for all European biosimilar G-CSFs (including XM02), FDA dossier for tbo-filgrastim (i.e. XM02), and journal publications
- Conclusions
  - All three (biosimilar) agents have similar safety profiles
  - None were statistically higher on safety parameters than what is known about originator filgrastim
  - What is known about filgrastim in general regarding safety can be extended to biosimilar filgrastim

European Biosimilar Safety: (Epoetin)

- Most data available to date suggest that the biosimilars approved in Europe have a similar safety profile to originator biosimilars
- Two cases of anti-epoetin antibodies have been reported with a European biosimilar, licensed for IV use only, that was administered subcutaneously
  - Syringe components likely contributed to protein aggregation

Examples of EMA Post-Marketing Surveillance Requirements

- Biosimilar epoetin
  - Monitoring for PRCA, thromboembolic events
  - Evaluation of subcutaneous use
  - Studies to evaluate safety and tolerability in certain indications
- Biosimilar filgrastim
  - Cooperation with the Severe Chronic Neutropenia International Registry
Response to Biosimilar Post-Marketing Surveillance Concerns

- “Robust post-marketing safety monitoring is an important component in ensuring the safety and effectiveness of biological products, including biosimilar therapeutic protein products”
- “...like any other biological products, FDA may take any appropriate action to ensure the safety and effectiveness of a proposed product, for example, requiring a post-marketing study to evaluate certain safety risks”


Follow-on Epoetins in “Less Regulated” Markets

- Pure red cell aplasia seen in a high number of patients in Thailand
- “Biosimilar” epoetin used from Argentina, China, South Korea, and India
- Globally, not all products identified as “biosimilars” truly meet that definition


Biosimilar Regulatory Review of Immunogenicity

- Essential to approval
- Patient populations and reactions evaluated must be pertinent to the molecule
- Requirements will differ by molecule
  - Filgrastim vs. epoetin vs. infliximab vs. rituximab
- Includes both pre-marketing and post-marketing requirements
- Similar standards in highly regulated countries such as E.U., Australia, Canada
  - Products from developing countries may not be adequately evaluated

Product Identification

- Key attributes to differentiate a biologic pharmaceutical
  - Brand name
  - NDC number
  - Lot number
  - Expiration date
  - Non-proprietary name?
- How easy is it for you to obtain these various data elements consistently?

Enoxaparin Example

- “After originator medicine’s loss of exclusivity, only 5% of spontaneous reports were processed by generic manufacturers”
- “…reports attributable to specific generics were approximately ninefold lower than expected based upon market share”
Key Questions

- Within your organization, what are the current processes for identification, documentation, and notification of adverse events related to drugs and biologics?
- How and by whom are adverse events reviewed within your institution? Does this review include pharmacist participation?

Key Questions (continued)

- How are patients educated to identify and report possible adverse drug events?
- What resources are available to assist in the provision of education to patients about adverse event identification and resolution?
- What aspects of routine patient care include a review of possible adverse drug events?

Key Questions (continued)

- How does your technology support your pharmacovigilance processes?
- What is your current rate of adverse events with existing commonly used medications?
Examples of Recently Approved “Breakthrough” Therapies

- Obinutuzumab
- Ibrutinib
- Sofosbuvir
- Ledipasvir/sofosbuvir
- Blinatumomab
- Nivolumab
- Palbociclib

Questions:
- Do we have adequate pharmacovigilance systems to identify novel adverse reactions of new molecular entities approved through expedited processes?

Key Steps in Effective Pharmacovigilance

- Ensure adverse event reporting program is in place
  - Definition and classification of adverse drug (biologic) events
  - Expectations and responsibilities for identification and reporting (multidisciplinary, including patients)
  - Mechanisms to screen reports consistently, look for trends, and report to manufacturers, FDA, others as appropriate
  - Education and awareness about the program

References:
Key Steps in Effective Pharmacovigilance (continued)

- Develop preventative interventions and strategies to decrease the incidence of adverse events
  - Proactive identification of high-risk patients
    - Use and integration of information systems (e.g., pharmacy and laboratory data)
  - “ADR indicator drugs”

Conclusions

- Improved pharmacovigilance for all medications – small molecule and large, originator biologic and biosimilar – is required
- Biosimilars in highly regulated markets are subject to stringent assessment of clinical immunogenicity
- However, effective surveillance is required as biosimilars are approved and marketed

Conclusions (continued)

- New biologic entities continue to be approved with limited safety profiles necessitating adequate monitoring
- Pharmacists are inherently responsible for the identification, documentation, and ideally prevention of adverse drug events
- Ineffective and/or inadequate pharmacovigilance will not be financially viable in the future state of health care
Which of the following would be an example of a biologic immune mediated adverse reaction?

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