Review Article

Biopharmaceuticals Breakthroughs and Beyond : Understanding and Mitigating Adverse Drug Reactions (ADRs)

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ABSTRACT

Biopharmaceuticals, while revolutionizing medicine, harbor potential for adverse reactions (ADRs)[1,2,3]. This presentation seeks to offer an exploration of adverse reactions (ADRs) linked to biopharmaceuticals. It will address the current scenario, emerging challenges, and essential pharmacovigilance strategies to enhance the safety of biopharmaceutical therapy.

This article is based on a comprehensive review of scientific literature published between 2017 and 2024. Relevant articles were identified in PubMed and Google Scholar using the keywords "biopharmaceuticals," "adverse reactions," "pharmacovigilance," and related terms. In addition to research papers, we reviewed case studies and reports from the World Health Organization (WHO) and the US Food and Drug Administration (FDA).

This is a narrative review aimed at providing a comprehensive overview of the current understanding of ADRs associated with biopharmaceuticals. We critically assessed the identified literature, analyzed trends and patterns in ADR reporting, and incorporated case studies to illustrate the challenges and complexities involved.

INTRODUCTION

Biopharmaceuticals are complex medicines made from living cells or organisms, often produced using cutting-edge biotechnological methods[4]. Biopharmaceuticals, advanced medicines, offer targeted treatment with fewer side effects than traditional medicine[5]. Despite contributing $163 billion globally, they pose a risk of adverse drug reactions (ADRs). Challenges in predicting preclinical to clinical outcomes and the potential for immunogenicity impact safety.[6,7] The rise in ADR reports worldwide underscores the need for vigilant pharmacovigilance, given the complexity of biological drugs and the difficulty in establishing causality.[8] Monitoring biopharmaceuticals closely is crucial for balancing effectiveness and safety in patient care.

Table 1: Examples of Biopharmaceuticals and their uses in Medical field [9,10]

Biopharmaceutical	Example	Uses
Monoclonal Antibodies	Adalimumab	Autoimmune diseases
Hormone	GH (Somatotrophin)	Turners syndrome
Vaccines	Moderna Covid-19 mRNA vaccine	SARS-CoV-2
Gene therapy	Zynteglo	Beta-thalassemia
Enzyme Replacement Therapy	Fabrazyme	Fabry disease
Modified T- Cells	CAR-T cell therapy	Immunotherapy

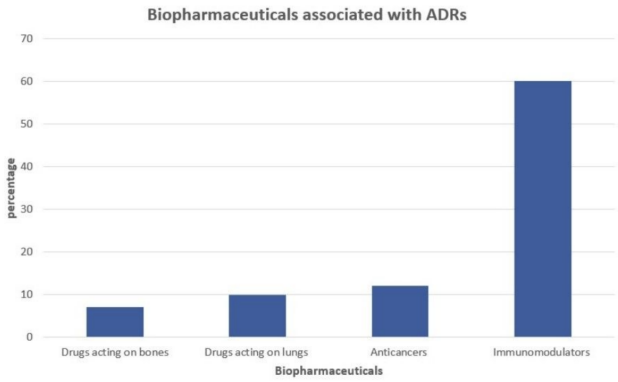
THE FLIP SIDE: UNVEILING ADRS ASSOCIATED WITH BIOPHARMACEUTICALS

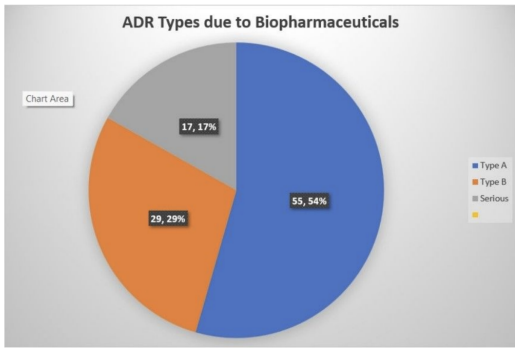
ADRs due to biopharmaceuticals are complex due to various factors, including their unique mechanisms of action, individual variability, long-term effects, complex immune responses difficulty in diagnosis, limited data, and reporting challenges e.g

• Immunological reactions

• Cytokine release syndrome
• Immunosuppression/infection
• Tumor lysis syndrome

* In a retrospective study of ADR reports from 2014 to 2019 in Columbia , The ADRs, groups of associated drugs, and affected organs were classified[12]





In total, 5,415 reports of ADRs associated with biological drugs were identified in 78 Colombian cities. A total of 76.1% of the cases corresponded to women. The majority were classified as type A (55.0%) and B (28.9%), and 16.7% were serious cases. The respiratory tract was the most affected organ system (16.8%), followed by the skin and appendages (15.6%). Antineoplastic and immunomodulatory drugs accounted for 70.6% of the reports, and the drugs related to the greatest number of ADRs were adalimumab (12.2%) and etanercept (11.6%).[10,11]

EMERGING CHALLENGES:

• **Under-reporting of ADRs:** Many ADRs associated with biopharmaceuticals go unreported, making it difficult to assess their true prevalence and identify new safety signals.

• **Complexity of biopharmaceuticals:** The complex nature of biopharmaceuticals makes it challenging to predict and understand their potential side effects.

• **Immunogenicity Issues:** Biopharmaceuticals may trigger immune responses, leading to the development of antibodies that can affect drug efficacy and safety. Monitoring and managing immunogenicity pose significant challenges in ADR surveillance.

• **Biosimilar Variability:** The increasing use of biosimilars introduces variability in drug responses. Monitoring ADRs becomes challenging as subtle differences between the reference biopharmaceutical and biosimilar may impact safety profiles.

• **Long-Term Effects:** Biopharmaceuticals often target chronic conditions, requiring long-term usage. Monitoring and understanding the potential ADRs over extended periods present challenges, especially considering evolving patient populations.

• **Personalized Medicine Challenges:** The trend towards personalized medicine using biopharmaceuticals raises challenges in predicting individual responses. Tailoring treatments to specific patient profiles adds complexity to ADR monitoring, requiring more precise and adaptable surveillance methods.

• **Microbiome alterations:** Biopharmaceuticals can disrupt the gut microbiome, leading to secondary effects like antibiotic-associated diarrhea, malnutrition, and inflammatory bowel disease [13, 14, 15]

MITIGATION STRATEGIES : ROLE OF PHARMACOVIGILANCE FOR BIOPHARMACEUTICALS

1 - Pre-market Assessment :
• Thorough pre-clinical testing: Examining potential risks based on the mechanism of action and target molecules.
• Comprehensive clinical trials: Evaluating safety and efficacy in diverse populations, including long-term follow-up.
• Risk management plans: Identifying potential risks and outlining strategies to mitigate them.

2 - Post-market Surveillance:
• Spontaneous adverse event reporting: Encouraging healthcare professionals and patients to report any suspected side effects.
• Active surveillance programs: Proactively monitoring specific safety concerns identified during pre-clinical or clinical stages.
• Pharmacoepidemiological studies: Evaluating safety in large populations using real-world data.

3 - Process of reporting ADRs in India[12]
MoH - Ministry of Health
NCP - National Centre for Pharmacovigilance(PV)
NDA - National Drug Authority
CDSCO - Central Drug Standard Control Organisation

4 - Risk Minimization Strategies:

• Clear and comprehensive labeling and prescribing information: Providing information about potential risks and precautions.
• Implementing specific actions to minimize identified risks: Restricting patient populations, monitoring requirements, or specific dosing recommendations.
• Educational programs: Educating healthcare professionals and patients about safe and effective use, recognizing, and reporting adverse events.

5 - Role of Regulatory Agencies:
Regulatory agencies like CDSCO can:

- Gather and analyze ADR reports from various sources.
- Communicate safety information about biopharmaceuticals to healthcare professionals and the public.
- Implement risk management strategies to mitigate identified safety concerns.

CONCLUSION

While biopharmaceuticals offer life-changing possibilities, their unique nature necessitates continuous improvement in ADR detection and mitigation. We must dedicate ongoing research and development efforts to refine and expand pharmacovigilance strategies, ensuring maximum benefit alongside minimized risks. Responsible risk management, informed by robust monitoring and proactive mitigation, must stand hand-in-hand with innovation in this transformative field. Only through this balanced approach can we harness the full potential of biopharmaceuticals while safeguarding patient safety.

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