ROLE OF IMMUNOGENICITY IN DRUG DEVELOPMENT

Afra Habib[1], Subuhi Anwar[2], Bishouno Bhowmick[3]

Department of Biochemistry[1], Department of Pathology[2], Department of Pharmacology & GP[3]

King George's Medical University, Lucknow, U.P., India-226003[1]

Era's Lucknow Medical College and Hospital, Era University, Sarfarazganj, Lucknow, U.P., India-226003[2].

American University of Barbados School of Medicine, Barbados-BB11100[3].

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Address for correspondence

Dr. Bishouno Bhowmick
Department of Pharmacology & GP
American University of Barbados School of Medicine, Barbados-BB11100.
Email: shimul_ssmc@yahoo.com
Contact no: +1-246-8284132

ABSTRACT

Immunogenicity, or a substance's potential to elicit an immunological response, is an important component in the creation of biologic and small molecule medications. Immunogenicity can impair the efficacy of biologics such as monoclonal antibodies, therapeutic proteins, and gene treatments, as well as pose possible safety issues and cause therapeutic failure. Understanding and predicting immunogenicity is thus a critical component of current pharmaceutical development. This study investigates the importance of immunogenicity in drug development, the variables that influence immunogenic reactions, methodologies for measuring and managing these responses, and regulatory implications. In addition, we cover recent advances in immunogenicity prediction and monitoring, as well as the issues associated with immunogenicity in emerging medication classes. The review looks at real-world examples that show how immunogenicity may significantly affect pharmacokinetics and pharmacodynamics. Additionally discussed are the regulatory standards governing the assessment of immunogenicity and the necessity of incorporating this data into regulatory filings. Lastly, future studies on immunogenicity will have an impact on the therapeutic impact landscape, which will have consequences for patient-centered care and precision medicine.

KEYWORDS: Immunity, Precision Medicine, Drug, Antibodies.

INTRODUCTION

The introduction of novel treatment modalities, including as monoclonal antibodies, Modern medicine has changed as a result of gene treatments and CAR T-cells. Cancer and genetic issues are among the many conditions for which these innovative medications provide more individualized and efficient treatments. Immunogenicity is one of the unique challenges that large molecule-based biologics and advanced cellular and gene therapies face, despite their potential.

Preclinical medication research and clinical trials have raised serious concerns about immunogenicity, or a medicinal substance's capacity to trigger an immune response in a patient. The immune system's ability to recognize and destroy foreign invaders is an essential defensive mechanism, but it may also detect and create defenses against therapeutic substances. which can result in safety issues, changed pharmacokinetics, and reduced effectiveness (1-2).The many facets of immunogenicity in preclinical drug development are examined in this review paper, with particular attention paid to its tactics, dangers, and consequences for biologics based on big molecules (3).

The Use of Immunogenicity in Drug Development

When developing immunogenicity of medicinal products is a crucial component that determines the safety and effectiveness of biological medications, such as gene therapies, CAR T-cell treatments, Both bi-specific and monoclonal antibodies. Anti-drug antibodies (ADAs) or neutralizing antibodies are produced when a medicinal substance triggers an immunological response in the body of the patient. The drug's safety, effectiveness, and commercial success may be impacted by this immune response (4). Using Model-Informed Methods to Evaluate Immunogenicity in Drug Development Targeting certain disease processes, such cancer cells or inflammatory pathways, is the goal of therapeutic treatments, especially big molecule-based biologics. The immune system may view these substances as alien when they are put into a patient's body since they are frequently complex molecules with distinctive structures. Antibodies against the therapeutic agent may be produced as a result of this immunological reaction to the perceived foreignness. Both the patient and the medication may suffer significant repercussions from the formation of ADAs (5).

Immunogenicity's Importance in Drug Development:

When developing new drugs, immunogenicity is crucial for a number of strong reasons.

- **Effectiveness:** The therapeutic agent's effectiveness may be diminished by the presence of ADAs. The drug's ability to successfully target the illness may be neutralized by ADAs. This may lead to disease progression, reduced clinical responses, and therapeutic failure.
- Safety: Immunogenicity may raise issues with safety. Adverse effects, including as autoimmune reactions, infusion-related reactions, and hypersensitivity reactions, might result from immune complexes that ADAs can generate when they attach to the medication. Patient injury and regulatory scrutiny may result from these safety concerns.
- Dose Adjustments: Clinicians may need to raise the medication dose in order to offset the effect of ADAs on drug effectiveness. This increases the likelihood of adverse outcomes and drives up treatment expenses.
- Treatment Discontinuation: Severe immunogenicity may occasionally cause a prospective medication candidate to stop taking their medication. This amounts to a significant loss in research and development expenditures as well as delays in providing patients with potentially life-saving therapies.
- Market Approval: When approving regulations such as the FDA (US Food) and Medicine Administration and the EMA (European Medicines Agency) carefully examine immunogenicity data. To secure regulatory approval, it is essential to exhibit a deep understanding of the immunogenicity profile and to establish effective management practices.
- Patient Variability: Not every patient responds to treatment with an ADA. The likelihood of an immunological response can be influenced by patient-specific variables, including genetics and prior exposure to comparable chemicals. Comprehending these elements is crucial for customized medical strategies.

A key factor in the creation of biological medications and treatments is immunogenicity. It is impossible to overestimate its influence on therapeutic efficacy, safety, and market acceptance. Protein engineering, formulation modification, and immunosuppressive treatments are some of the tactics used by drug developers to successfully handle immunogenicity. To guarantee that cutting-edge medicines adhere to the strictest safety and effectiveness guidelines while getting to the people who require them, researchers and pharmaceutical firms must continue to be careful in evaluating and minimizing the impacts of immunogenicity as it continues to shape (4, 6).

Therapeutic agent types: Therapeutic agents, which provide novel ways to treat a variety of illnesses, have completely transformed medicine. Among these, Gene and CAR T-cell therapies, as well as big molecule-based biologics, have revolutionized medical care. An outline of these therapeutic agents will be given in this part, together with information on their mechanisms and importance in contemporary medicine.

- Biologics Based on Large Molecules: Antibodies that are monoclonal and bispecific mAbs, or monoclonal antibodies: Large protein molecules known as monoclonal antibodies are directed against certain antigens, such as soluble components of disease processes or proteins found on the cell surface. They are useful instruments in precision medicine since they are tangible and have little toxicity. mAbs can function in a number of ways, such as:
- Neutralization: mAbs have the ability to stop a particular molecule's action, preventing it from contributing to the development of a disease. For instance, monoclonal antibodies such as trastuzumab block the development of breast cancer cells by targeting their HER2 receptors.
- Immune Activation: Certain monoclonal antibodies, also referred to as inhibitors of immunological checkpoints (e.g., nivolumab and pembrolizumab), stimulate the ability of the immune system's ability to identify and combat cancerous cells.
- Drug Delivery: By acting as drug transporters, mAbs can deliver harmful payloads precisely to the locations of illness. ADCs, or antibody-drug conjugates, employ this strategy.
- Engineered bispecific antibodies are capable of simultaneously engaging with two different antigens. This mechanism amplifies the immune system's ability to detect and eliminate atypical cells by creating a bridge between the target cells and immune cells. In cancer treatment, these antibodies have exhibited encouraging results by directing T-cells to attack tumor cells.
- The specificity of CAR T-cells is derived from their ability to recognize unique antigens on cancer cells, thus ensuring targeted intervention in tumor destruction.

- The binding of CAR T-cells to malignant cells post-injection initiates a robust immune response, enabling the immune system to effectively target and eliminate the tumors.
- Persistence: For long-term monitoring against cancer recurrence, CAR T-cells can remain in the body. When it comes to treating hematologic malignancies like some forms of leukemia and lymphoma, CAR T-cell treatments have demonstrated impressive results. There are still difficulties, though, including as controlling serious side effects and extending its use to solid tumors.

Gene Therapies: By changing a patient's cells' genetic composition, gene therapy is a revolutionary method for curing or preventing illnesses. To improve treatment results or address congenital anomalies, it entails adding, deleting, or altering genes inside a patient's cells. There are two primary categories of gene therapies:

- Gene therapy by somatic means: In order to cure illnesses in patients without changing their germ line, this targets non-reproductive cells. An FDA-approved gene therapy called Luxturna, for instance, treats hereditary retinal degeneration by giving retinal cells a functioning copy of a gene.
- By altering the DNA in reproductive cells, germline gene therapy can have an effect on subsequent generations. It is not often done and has serious ethical and safety issues. Gene treatments have enormous promise for treating uncommon illnesses, genetic problems, and even some acquired ailments. They provide the possibility of curative or long-lasting therapy, but issues including immunological responses, vector safety, and long-term monitoring need to be resolved.
- Gene treatments, CAR T-cell therapies, and large molecule-based biologics are examples of innovative therapeutic approaches that are changing the medical landscape. Patients with diseases that were previously incurable now have new hope thanks to their expanding specialized mechanisms and applications. To optimize their advantages for global healthcare, researchers, physicians, and legislators must overcome the intricate safety, cost, and accessibility issues that accompany these advancements.

Evaluation of Immunogenicity: Particularly when developing gene therapies, CAR T-cell therapy, and large molecule-based biologics, immunogenicity evaluation is essential. It entails assessing the likelihood that these therapies may cause patients to mount an immunological response, which could have serious clinical repercussions. In addition to discussing the significance of predictive immunogenicity tests, this section will examine the techniques and resources utilized for immunogenicity evaluation throughout preclinical research (7-10).

Tools and Techniques for Evaluating Immunogenicity in Preclinical Development:

The enzyme-linked immunosorbent assay, or ELISA, is: The detection and measurement of antibodies to therapeutic proteins is a common use for ELISA. In preclinical research, scientists can administer the experimental medication to animal models and use ELISA to track the formation of anti-drug antibodies (ADAs). This aids in determining how immunogenic the treatment may be (7, 11).

To assess the immune cells' reaction, cell-based tests expose them to the therapeutic substance. As an illustration, tests for lymphocyte proliferation can quantify how many immune cells proliferate in response to a treatment. These tests reveal information on the immune system's response to the therapy (12).

SPR, or surface plasmon resonance, is a potent technique for researching how medicinal substances and antibodies bind together. It can assist in determining the probability of immunogenicity by revealing the kinetics and affinity of these interactions (13).

Mass spectrometry: Peptides produced by the breakdown of the therapeutic protein can be identified and measured using mass spectrometry. Any changes to the peptide profile may be a sign of possible immunogenicity issues.

In Silico Predictive Models: By examining elements such protein sequence, post-translational changes, and HLA binding affinity, computational models are able to forecast the possible immunogenicity of medicinal drugs. These models aid in risk assessment and early screening (4).

The significance of assays for predictive immunogenicity: For a number of reasons, predictive immunogenicity tests are crucial in directing the creation of therapeutic medicines.

Early Risk Assessment: During the early stages of drug development, researchers can detect immunogenicity hazards thanks to predictive tests. Making important decisions on the ongoing development of a potential medication requires the use of this knowledge.

Optimizing Therapeutics: Researchers can alter the structure or formulation of a therapeutic drug to lessen its capacity to trigger an immune response by knowing the elements that contribute to immunogenicity. Drug effectiveness and safety may be improved by this modification.

The role of predictive testing in patient safety: is significant, as it reduces the chances of adverse events related to immunogenicity. When a treatment is expected to elicit antibodies that could undermine its efficacy or provoke negative responses, it allows for further evaluation or alteration to minimize potential risks (6, 10).

Regulatory Compliance: When developing new drugs, regulatory bodies such as the FDA and EMA want thorough immunogenicity evaluations. Approval is facilitated by predictive tests, which assist sponsors in fulfilling these regulatory obligations (7).

Cost-Efficiency: Early detection of potential immunogenicity issues can result in significant cost savings. It facilitates astute decision-making, avoiding expensive post-marketing issues or late-stage failures. Testing for preclinical immunogenicity is crucial to the development of new drugs, especially gene treatments, CAR T-cell treatments, and big molecule-based biologics. Potential immunogenicity issues are proactively addressed by combining experimental techniques with prediction testing. By streamlining the medication development process and improving the safety and effectiveness of therapeutic agents, this makes it easier to provide cutting-edge medicines to patients. (6,10)

Immunogenicity Influencing Factors: Developing safe and efficient therapies requires an understanding of the factors influencing the immunogenicity of medicinal drugs. The term "immunogenicity" explains how a medicinal substance might cause a patient's immune system to react, usually resulting in the development of antibodies against the agent. The immunogenicity of therapeutic agents can be affected by a number of circumstances, and these aspects are important in determining how to design new drugs. We shall examine the main elements that influence immunogenicity in this section:

The structure of proteins:

The primary structure: One of the primary factors influencing immunogenicity is the therapeutic protein's amino acid composition. An immunological reaction can be more likely to be triggered by particular lines.

Secondary and Tertiary Structure: A protein's immunogenicity may be impacted by modifications to its secondary and tertiary structures, which may arise as a result of production procedures or storage circumstances. Aggregation or misfolding may increase the immunogenicity of the protein.

PTMs, or post-translational modifications:

Glycosylation: Proteins' immunogenicity can be greatly impacted by the addition of carbohydrate chains. The stability of the protein and its capacity to elicit an immunological response can be affected by the kind and pattern of glycosylation.

Deamidation: Protein structure can alter and immunogenicity might be impacted when asparagine or glutamine residues are converted to aspartic or glutamic acid.

Factors Associated with Patients:

Genetics: Human leukocyte antigen (HLA) genotypes are the primary genetic factors that influence the tendency of a person to mount an immune response against a therapeutic treatment is influenced by genetic predispositions. Specific HLA alleles may facilitate a more efficient presentation of the therapeutic protein's peptides to the immune system.

Immune Status: Individuals undergoing organ transplantation or chemotherapy who have weakened immune systems may react differently to therapeutic drugs in terms of immunogenicity. Antibodies to biologics, on the other hand, could be more common in people with autoimmune illnesses.

Formulation and Delivery:

Components of the Formulation: Immunogenicity may be impacted by excipients, stabilizers, and preservatives included in a medicinal formulation. Certain additions may alter the protein's stability or cause an immunological reaction.

Administration Route: A therapeutic agent's immunogenicity may be impacted by the way it is delivered. Compared to intravenous delivery, subcutaneous or intramuscular injections may have distinct immunogenic characteristics.

Production Procedures:

The decision regarding which cell lines: to employ for protein expression may affect immunogenicity through its impact on the quantity of host cell proteins and residual DNA found in the end product.

Purification Techniques: In order to separate the therapeutic protein, purification procedures may add impurities or cause structural alterations that affect immunogenicity. Designing therapeutic drugs with lower immunogenic potential requires an understanding of these parameters. It makes it possible to create plans to reduce the risks of immunogenicity, such changing the structure or formulation of the protein, using predictive immunogenicity assays, and performing preclinical research in appropriate animal models. Researchers and developers may enhance the safety and effectiveness of medicinal medicines by addressing these aspects, which will eventually benefit patients and advance the biopharmaceuticals industry (14-15).

Pharmacokinetic and pharmacodynamic effects of immunogenicity and PK/PD:

When it comes to medication development and clinical results, immunogenicity—the ability of medicinal substances to elicit immune responses—is crucial. It can significantly impact pharmacokinetics (PK) and pharmacodynamics (PD), affecting the way medications interact with target molecules as well as how they are absorbed, transported, metabolized, and removed. In-depth discussion of the complex connection between immunogenicity and PK/PD will be covered in this part, along with instances from actual life when immunogenicity impacted medication effectiveness.

Effect on Pharmacokinetics (PK):

- **Modified Drug Absorption:** Immunogenicity may have an impact on how well therapeutic drugs are absorbed. Neutralizing antibodies, for instance, can lower the Bioavailability of oral or subcutaneously administered biologics. In some situations, higher dosages could be needed to reach the appropriate medication levels.
- Modified Distribution: Immunogenicity may have an effect on how medications are distributed throughout the body. Antibodies can alter a drug's distribution profile when they attach to it. This may result in less than optimal therapeutic levels at the intended location and impair the drug's ability to penetrate tissue.
- Elimination and Metabolism: Anti-drug antibodies (ADAs) have the ability to obstruct the drug's removal and metabolism. A shorter half-life and the need for more frequent dosage can result from ADAs' ability to speed up the drug's clearance rate.

Pharmacodynamics (PD) Impact: Decreased Drug Efficacy Immunogenicity can counteract a drug's therapeutic impact by attaching itself to it and blocking its ability to interact with its target. Even at high doses, the medicine may become useless due to its neutralization.

- Immunological Response Induction: Certain medications have the potential to trigger immunological responses, which might result in unfavorable PD consequences. For example, cytokine release syndrome (CRS), a documented adverse event of CAR T-cell treatments, occurs when immune cell activation causes an excessive release of cytokines, which may result in serious adverse effects (16-17).

Real-World Illustrations

- Infliximab, classified as a monoclonal antibody, is indicated for the treatment of autoimmune diseases such as rheumatoid arthritis and Crohn's disease. However, the formation of anti-drug antibodies (ADAs) can arise, which may compromise the drug's effectiveness and contribute to the failure of the treatment regimen.
- Neutralizing Antibodies with Erythropoietin (EPO): Some individuals may develop neutralizing antibodies as a result of EPO, a hormone that promotes the synthesis of red blood cells. A reduced response to therapy results from these antibodies' reduction of the drug's efficacy.
- CAR T-Cell treatments: In the treatment of some malignancies, CAR T-cell treatments have demonstrated exceptional effectiveness. But they can also cause serious immunological reactions, such as CRS and neurotoxicity, which can be fatal if left untreated. (9-10)

Strategies for Risk Mitigation: Handling Immunogenicity:

Drug research and clinical applications are significantly hampered by immunogenicity, the ability of medicinal substances to elicit immunological responses. Numerous risk-reduction techniques have been created to lessen the effects of immunogenicity.

Engineering Proteins:

- Deimmunization: The goal of protein engineering methods is to alter therapeutic proteins' structures in order to lessen their immunogenicity. Modifying certain protein areas that are susceptible to immune recognition is known as deimmunization. Site-directed mutagenesis, which involves replacing amino acids to get rid of T-cell epitopes—the main triggers for the immunological response—can accomplish this.
- Humanization: is the process of substituting human sequences with non-human ones in therapeutic antibodies while maintaining the antibody's therapeutic effects. This lessens the possibility that non-human epitopes may trigger an immunological response.
- Fusion Proteins: Therapeutic proteins can be made less immunogenic by combining them with non-immunogenic domains or antibodies. These fusion proteins can protect against the detecting systems of the immune system (18-19).

Development of Formulations:

Stabilization: The goal of formulation development is to stabilize therapeutic substances so they don't aggregate or degrade and cause immunological reactions. An appropriate formulation can minimize the exposure of immunogenic epitopes while preserving the drug's structural integrity.

Selection of Excipients: In medication formulations, excipients are essential. By reducing protein aggregation and improving stability, excipient selection can reduce immunogenicity. The release profile of the medication can also be altered by excipients, which lowers the possibility of immunological recognition.

Treatments for Immunosuppression:

- Combined Immunosuppressive Drug Administration: Immunosuppressive medications may occasionally be used in conjunction with therapeutic treatments to reduce immunological responses. Gene treatments and organ transplantation are two areas where this strategy is very pertinent. Corticosteroids and calcineurin inhibitors are examples of immunosuppressants that can lower the risk of rejection by lowering the activity of the immune system.
- Immunological tolerance to the therapeutic substance is the goal of tolerance induction techniques. Numerous strategies, such as regulatory T-cell (Treg) treatment and oral or nasal tolerance induction, can accomplish this. The goal of these strategies is to teach the immune system to accept the medicinal protein.
- Corticosteroid Prophylaxis: When delivering highly immunogenic treatments, prophylactic corticosteroid usage is used in some clinical contexts to minimize possible immunological responses. The safety and effectiveness of therapeutic agents, especially large molecule-based biologics like gene therapies, CAR T-cell therapies, and monoclonal antibodies, depend significantly on the management of immunogenicity. Strategies for risk mitigation include formulation improvement to improve stability, immunosuppressive treatments where required, and protein engineering to decrease immunogenic epitopes. When used carefully, these tactics can greatly increase the efficacy and safety of biologics based on big molecules, opening the door to more potent therapies for a range of illnesses.

Gene therapies and immunogenicity:

- Viral Vector-Mediated Delivery: Viral vectors such as lentiviruses or adeno-associated viruses (AAVs) are used in many gene therapies to introduce therapeutic genes into target cells. These vectors can trigger immunological responses in addition to effectively transferring genes.
- Host Immune Recognition: The host's immune system may identify viral vectors as foreign invaders once they are administered. Both innate and adaptive immune responses may be triggered by this identification.
- Neutralizing Antibodies: Neutralizing antibodies against viral vectors that are either pre-existing or developed as a result of treatment may make gene therapy less effective. The therapeutic gene cannot be delivered to the target cells by the vector when it is neutralized.
- Cell-Mediated Immune Responses: Vector proteins or vector-infected cells can cause T-cell reactions. The length of gene expression may be restricted by this cellular immunological response, which might also raise safety issues (22-23).

Reduced Immunogenicity in Gene Treatments:

- Capsid Engineering: By changing the outer shell, a process known as capsid engineering, scientists are attempting to reduce the immunogenicity of the viral vector.
- Immunosuppressive Techniques: To reduce immune responses, immunosuppressive medications and gene treatments may be used in combination. To combine immune suppression with maintaining therapeutic efficacy and patient safety, however, cautious monitoring is needed.
- Other Types of Vectors: Direct genome editing approaches like CRISPR-Cas9 or non-viral delivery methods like lipid nanoparticles are being investigated as potential substitutes for viral vectors. These techniques seek to reduce the immunological reactions brought on by viral vectors.
- Patient Monitoring: To quickly identify and treat any immune-related side effects, patients undergoing gene therapy must be regularly monitored. Although gene treatments provide innovative therapeutic alternatives, immunogenicity is still a crucial factor. Managing immunogenicity involves the use of immunosuppressive techniques, capsid modification, and viral vector selection. The objective of this field's ongoing research is to create gene treatments that are both extremely efficacious

and less immunogenic so that they may be successfully and safely incorporated into clinical practice (6, 18-21).

Managing the Regulatory Environment for Immunogenicity Evaluation:

For large molecule-based biologics, gene therapies, and Drug development depends on the regulatory framework governing immunogenicity assessment, especially for CAR T-cell therapies. Various regulatory bodies, including the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA), have established strict guidelines to ensure that these state-of-the-art treatments meet high standards of safety and effectiveness. Here, we give a quick rundown of the regulatory environment and stress how important it is to address immunogenicity in regulatory filings.

Key Regulatory guidelines

- The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has established recommendations that guide the assessment of immunogenicity in biologics. These guidelines, particularly ICH S6R1 and ICH S6R2, create a framework for analyzing immune responses and their potential consequences for therapeutic efficacy and patient safety.
- FDA Advice: In materials pertaining to immunogenicity evaluation, the FDA provides guidance on how to plan studies, create assays, and evaluate findings. These recommendations help pharmaceutical companies handle immunogenicity issues in preclinical and clinical settings.(11)
- EMA Requirements: For biologics requesting marketing authorization in Europe, the EMA also offers guidelines on immunogenicity evaluation. These specifications stress the necessity of doing a thorough assessment of immunogenicity risks (7) and are in line with international standards.

Managing immunogenicity in regulatory submissions is crucial:

- Safety Assurance: Patient safety is given top priority by regulatory bodies. To guarantee that therapeutic drugs do not cause detrimental immune responses that might jeopardize patient health, it is essential to comprehend and manage immunogenicity concerns.
- Efficacy Assessing: The effectiveness of therapeutic drugs may be impacted by immunogenicity. Data showing that the medication produces the desired effect in spite of possible immunological reactions must be included in regulatory applications. Strong assays and a comprehensive comprehension of the immunogenicity profile are necessary for this.
- Risk Mitigation: Drug developers are expected by regulatory agencies to put methods in place to reduce the risks of immunogenicity. This might entail employing suitable immunosuppressive treatments, creating biologics with less immunogenic potential, and keeping an eye out for immune-related side effects in patients.
- Patient-Centric Approach: The significance of patient-centric treatment is acknowledged by regulatory bodies. Drug developers may help create individualized treatment plans that meet the needs of each patient by evaluating and controlling immunogenicity, which will guarantee the efficacy and safety of the medication.

The development and approval of gene treatments and CAR T-cell therapy, and biologics based on big molecules depend heavily on regulatory criteria and recommendations for immunogenicity evaluation. In addition to increasing the likelihood of regulatory clearance, heeding these recommendations ensures the therapeutic agent's clinical utility and, more importantly, safeguards patient health. Regulatory agencies must be consulted early in the drug development process, and immunogenicity issues must be thoroughly addressed at every stage of the product life cycle (20).

Future Prospects for Drug Development and Immunogenicity Research:

Within the realm of drug research, immunogenicity is still a vibrant and developing topic that has promise for many new developments in the future. In the upcoming years, academics and pharmaceutical firms are anticipated to focus on the following important areas:

- Precision Medicine in Immunogenicity: Personalized methods of managing immunogenicity are becoming possible because to developments in proteomics and genomes. A major emphasis will be on customizing therapies based on the individual traits of every patient and their genetic vulnerability to immunogenic responses.Advanced Analytics and large Data: Artificial intelligence and large data analytics will be used more often in immunogenicity monitoring and prediction. Patients who are more likely to acquire anti-drug antibodies can be identified with the use of predictive algorithms.
- Biosimilar Development: Knowing the immunogenicity profiles of biosimilars in

comparison to reference biologics will remain a crucial topic of research as they proliferate. It will be crucial to develop methods for proving biosimilarity while reducing immunogenicity variations.

- Next-Generation Biologics: Research and development will continue to produce Better protein engineering and reduced immunogenicity in subsequent-generation biologics, and increased therapeutic effectiveness. Novel delivery methods, different scaffolds, and improved targeting mechanisms are a few examples of innovations.
- Cell and Gene treatments: CAR T-cell and gene treatments depend on the development of strategies to reduce immunogenic reactions to modified cells and vectors. Creating synthetic biology strategies to reduce host immune responses is part of this.
- Advanced Assay Techniques: It will be crucial to create assays that are more sensitive and specific in order to determine immunogenicity. To learn more about immune responses, this involves applying high-throughput methods, single-cell analysis, and microfluidics.
- Immunomodulation Strategies: One promising approach to managing immunogenicity will be to look at cutting-edge immunomodulation techniques like immune checkpoint inhibitors or immunological tolerance induction.
- Regulatory Evolutions: Regulatory bodies will probably keep improving standards and procedures for determining immunogenicity, particularly for new modalities. Global regulators' alignment will continue to be crucial.
- Patient-Centric Approaches: It is becoming more popular to involve patients in the tracking and control of immunogenicity. Feedback and results from patients can improve treatment choices and offer useful information.
- Long-Term Safety Monitoring: Post-marketing monitoring and long-term safety monitoring of biological products, which includes assessing the potential for late-onset immunogenicity, will become increasingly important.

Next-generation biologics, biosimilar development, advanced analytics, precision medicine, and innovative immunomodulation methods will be the main areas of focus for this field's future. Cooperation among regulatory agencies, business, and academia will keep advancing our knowledge of and ability to handle immunogenicity issues in drug development (4, 31).

DISCUSSION

When developing novel pharmacological drugs, it is important to carefully evaluate not only their safety profiles, pharmacodynamics, and pharmacokinetics, but also their capacity to elicit an immunological response. The tendency of a medication to cause the production of antibodies, especially neutralizing antibodies (Nabs), is known as immunogenicity. This can have negative implications on the medication's pharmacological efficacy. Despite being a well-known issue with biologics, immunogenicity is also becoming more and more relevant in the creation of small molecule medications. A major problem that affects patient safety and medication effectiveness is immunogenicity. The year 1986 marked a significant milestone when the Food and Drug Administration (FDA) approved the inaugural monoclonal antibody therapy featuring chimeric sequences derived from both human and mouse sources. Following this landmark event, pharmaceutical companies have made concerted efforts to enhance the pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity characteristics of therapeutic proteins and antibodies, largely through the optimization of their sequences. Recent innovations in structural and chemical modifications, such as PEGylation, glycosylation, and lipidation, have facilitated the creation of multidomain biotherapeutics (MDB) that bolster stability, aggregation, adsorption, and degradation, alongside improvements in PK, PD, and immunogenicity. An illustrative example of these advancements is the 2013 approval of a recombinant anti-hemophilic factor VIII, aimed at treating and preventing bleeding episodes in individuals with hemophilia A (32-35).

A method for monitoring immunogenicity was developed and applied to support the clinical development program of a novel complex biologic agent during its early clinical development phases. In crafting the strategy for a multidomain biotherapeutic of this type, various considerations were taken into account, as each conjugation results in a distinct domain interface. Risk assessment is based on a range of factors, including the presence of endogenous equivalents, the development and availability of pharmacodynamic biomarkers, and the cell epitopes of T and B lymphocytes (36-41). At the commencement of the first-in-human (FIH) study for the drug under consideration, there were no trustworthy clinical pharmacodynamic biomarkers available for target engagement or response prediction, which are vital for determining safety and efficacy. The ability of GDF15 to suppress food intake, which is integral to energy regulation and is considered a key factor in metabolic

disorders, prompted the establishment of a detailed immunogenicity strategy. Our analysis of the drug as a high-risk candidate regarding immunogenicity risk assessment validated the comprehensive immunogenicity strategy that was both proposed and implemented, especially in light of its chemical alterations (41).

CONCLUSION

To sum up, immunogenicity is essential for creating therapeutic agents, especially gene therapies, CAR T-cell treatments, and biologics based on big molecules. With its emphasis on its importance, evaluation techniques, and consequences for pharmacokinetics, pharmacodynamics, and patient safety, this thorough analysis has shed light on the complex nature of immunogenicity. However, with the use of advanced instruments, predictive tests, and risk reduction techniques, immunogenicity—a complicated phenomenon—can be anticipated and controlled. A new age of tailored therapeutics is being ushered in by the developing field of precision medicine, which provides exciting opportunities to customize therapies and reduce immunogenic reactions. Regulatory bodies are essential to maintaining strict guidelines for immunogenicity evaluation as the pharmaceutical sector innovates. To further our knowledge of immunogenicity and its management, cooperation between stakeholders-including patients, researchers, doctors, and regulatory agencies-will continue to be crucial. Exciting outcomes are anticipated from future avenues in immunogenicity research, including patient-centric methods, next-generation biologics, and sophisticated analytics, which, when combined, might revolutionize the sector and enhance patient outcomes. A better knowledge of immunogenicity will continue to be crucial in this changing environment for the safe and effective development of medications that will ultimately benefit patients and push the limits of contemporary medicine.

REFERENCES

1. Harding FA, Stickler MM, Razo J, et al. The immunogenicity of humanized and fully human antibodies: Residual immunogenicity resides in the CDR regions. MAbs. 2010; 2: 256-265.
2. Akabari AH, Patel S, Vaghela N, et al. Recent Application of Nanotechnology for Cancer Immunotherapy and Its Future Prospects. Int J Immunol Immunother. 2023; 10: 69.
3. Hanna E, Rémuzat C, Auquier P, et al. Gene therapies development: slow progress and promising prospect. J Mark Access Heal Policy. 2017; 5: 1265293.
4. Shakhnovich V, Meibohm B, Rosenberg A, et al. Immunogenicity in Clinical Practice and Drug Development: When is it Significant?. Clin Transl Sci. 2020; 22: 219-223.
5. Ilinskaya AN, Dobrovolskaia MA. Understanding the immunogenicity and antigenicity of nanomaterials: Past, present and future. Toxicol Appl Pharmacol. 2016; 299: 70-77.
6. Sauna ZE, Jawa V, Balu-Iyer S, et al. Understanding preclinical and clinical immunogenicity risks in novel biotherapeutics development. Front Immunol. 2023; 14: 1664-3224.
7. Emea. Committee For Medicinal Products For Human Use (CHMP) Draft Guideline On Immunogenicity Assessment Of Biotechnology-Derived Therapeutic Proteins Draft Agreed By BMWP. cited 2006. Available from: www.ema.europa.eu/contact
8. Rosenberg AS, Sauna ZE. Immunogenicity assessment during the development of protein therapeutics. J Pharm Pharmacol. 2018; 70(5): 584-594.
9. Dingman R, Balu-Iyer SV. Immunogenicity of Protein Pharmaceuticals. J Pharm Sci. 2019; 108(5):1637-1654.
10. Dimitrov DS. Therapeutic proteins. Methods Mol Biol. 2012; 899:1-26.
11. Pineda C, Hernández G.C, Jacobs IA, et al. Assessing the Immunogenicity of Biopharmaceuticals. BioDrugs. 2016; 30(3):195-206.
12. Potthoff B, McBlane F, Spindeldreher S, et al. A cell-based immunogenicity assay to detect antibodies against chimeric antigen receptor expressed by tisagenlecleucel. J Immunol Methods. 2020; 476: 112692.
13. Beeg M, Nobili A, Orsini B, et al. A Surface Plasmon Resonance-based assay to measure serum concentrations of therapeutic antibodies and anti-drug antibodies. Sci Rep. 2019; 9(1): 2064.
14. Schellekens H. Factors influencing the immunogenicity of therapeutic proteins. Nephrol Dial Transplant. 2005; 20: 63-69.
15. Aryal S. Factors affecting Immunogenicity. Microbe Notes. 2021.
16. Smith A, Manoli H, Jaw S, et al. Unraveling the Effect of Immunogenicity on the PK/PD, Efficacy, and Safety of Therapeutic Proteins. J Immunol Res. 2016; 2016: 2342187.
17. Chirmule N, Jawa V, Meibohm B. Immunogenicity

to therapeutic proteins: Impact on PK/PD and efficacy. AAPS J. Springer. 2012; 14: 296–302.

18. Jogalekar MP, Rajendran RL, Khan F, et al. CAR T-Cell-Based gene therapy for cancers: new perspectives, challenges, and clinical developments. Front Immunol. 2022; 13: 925-985.
19. NCI Editors. CAR T Cells: Engineering Immune Cells to Treat Cancer - NCI (Internet). Natl Cancer Inst. 2022 (cited 2023 Sep 10). Available from: https://www.cancer.gov/about-cancer/treatment/research/car-t-cells
20. Vandivort TC, Horton DB, Johnson SB. Regulatory and strategic considerations for addressing immunogenicity and related responses in biopharmaceutical development programs. J Clin Transl Sci. 2020; 4(6): 547-555.
21. Varin J, Morival C, Maillard N, et al. Risk mitigation of immunogenicity: A key to personalized retinal gene therapy. Int J Mol Sci. 2021; 22(23): 12818.
22. Yang T, Braun M, Lembke W, et al. Immunogenicity assessment of AAV-based gene therapies: An IQ consortium industry white paper. Mol Ther Methods Clin Dev. 2022; 26: 471-494.
23. Ertl HCJ. Immunogenicity and toxicity of AAV gene therapy. Front Immunol. 2022; 13: 975803.
24. FDA. International Regulatory Harmonization | FDA (Internet). 2020 (cited 2023 Sep 10). Available from: https://www.fda.gov/drugs/cder-international-program/international-regulatory-harmonization
25. Atzeni F, Sarzi-Puttini P, Doria A, et al. Potential off-label use of infliximab in autoimmune and non-autoimmune diseases: A review. Autoimmun Rev. 2005; 4(3): 144-152.
26. Lapadula G, Marchesoni A, Armuzzi A, et al. Adalimumab in the Treatment of Immune-Mediated Diseases. Int J Immunopathol Pharmacol. 2014; 27(1 Suppl): 33-48.
27. Introduction - Clinical Review Report: Migalastat (Galafold) - NCBI Bookshelf (Internet). (cited 2023 Sep 10). Available from: https://www.ncbi.nlm.nih.gov/books/NBK567517/
28. Guttmann A, Krasnokutsky S, Pillinger MH, et al. Pegloticase in gout treatment - safety issues, latest evidence and clinical considerations. Ther Adv Drug Saf. 2017; 8(12): 379-388.
29. Kozma GT, Shimizu T, Ishida T, et al. Anti-PEG antibodies: Properties, formation, testing and role in adverse immune reactions to PEGylated nano-biopharmaceuticals. Adv Drug Deliv Rev. 2020:154-155:163-175.
30. Scott LJ. Etanercept: a review of its use in autoimmune inflammatory diseases. Drugs. 2014; 74(12): 1379-410.

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Orcid ID:

Afra Habib - https://orcid.org/

Subuhi Anwar - https://orcid.org/

Bishouno Bhowmick - https://orcid.org/

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