Review Article

Biovigilance: A Global Perspective

Sukhjinder Singh, Shammy Chandel[1], Phulen Sarma, Dibbanti Harikrishna Reddy, Abhishek Mishra, Subodh Kumar, Prasad Thota, Kotni Murali, Ajay Prakash, Bikash Medhi

Departments of Pharmacology and [1]Neurosurgery, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Abstract

A biological is a substance which either comprises, contains, or is derived from human cells or human tissues. The use of biological products is associated with the risk of infection transmission, allergic reactions, and other adverse events (AEs). The science and activities relating to the detection, assessment, understanding, and prevention of AEs or any other problems related to biological products (blood, cells, tissues, organs, and vaccine in international perspective) are termed as biovigilance. With more and more biologicals being marketed and the rapid revolutionary changes in transplant-related services, the importance of biovigilance is increasing day by day. Although specific types of vigilance systems (pharmacovigilance and materiovigilance) exist, activities related to "biovigilance" are still in an infancy stage. Many developed countries such as the USA, Europe, and Australia have implemented nationwide biovigilance programs. In India, the National Institute of Biologicals, in collaboration with the Indian Pharmacopoeia Commission, has launched the Biovigilance Programme of India. In this article, the biovigilance systems of different countries across the globe have been reviewed along with highlights of the current biovigilance needs.

Keywords: Adverse events, biological products, biovigilance

Address for correspondence: Prof. Bikash Medhi, Department of Pharmacology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh - 160 012, India.
E-mail: drbikashus@yahoo.com

INTRODUCTION

Biovigilance is the surveillance system for tracking of adverse events (AEs) in recipients and donors associated with the use of biological products (blood, blood products, cells, tissues, organs, and vaccine).[1] The US biovigilance network defines "biovigilance" as a science for detection, gathering, and analysis of information regarding the untoward and unexpected events associated with blood collection and transfusion, transplant of cells, tissues, and organs. This systematic surveillance system is required to issue safety alerts in a timely manner and exchange of updated valid information to promote safe and efficacious transfusion and transplantation.[2] In other words, biovigilance is the extension of hemovigilance, which incorporates surveillance of AEs and untoward events associated with other biological products in addition to blood and blood-derived products.[1]

Biological products are contributing enormously to the improvement of quantity and quality of life (QOL). Numerous disease treatment modalities highlight the importance of biologicals in health-care management.[3,4] The increasing use of these biological products globally brings the inherent risk of transmission of donor-derived diseases, infections, and immunologic reactions in recipients.[3,5]

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Although biovigilance has been in discussion in recent times, most review articles tend to focus on either transplantation or hemovigilance. In this current review, we have covered the overall subdomains and spectrum of biovigilance, current needs, and future perspective [Figure 1].

RISKS ASSOCIATED WITH USE OF BIOLOGICS

The most common infections or diseases associated with the use of biologics includes HIV infection, Hepatitis-A, Hepatitis-B, Hepatitis-C, human T-cell lymphotrophic virus type-I and type-II infection, rabies virus, West Nile virus (WNV), Zika virus, lymphocytic choriomeningitis virus, streptococcal infections, *Mycobacterium tuberculosis*, malaria, babesiosis, and *Trypanosoma cruzi* infection.[1,2,5,6] Organ transplantation is also associated with the transmission of various types of malignancies.[6,7] Immunogenic reactions (allergic reactions) are less frequent but can be life-threatening or even fatal.[4,8] Table 1 highlights the different risks associated with the use of biological materials.

WHAT IS THE NEED FOR BIOVIGILANCE SYSTEM?

The risk of transmission of infections, allergic reactions, and other AEs associated with the use of biological products pose a big challenge for health-care professionals.[2,8,20] Defects or faults in the current manufacturing processes and procedures can also transmit infections or infectious diseases to recipients. Examples include the development of sepsis on receipt of bacteria-contaminated albumin due to a crack in the vial, AEs associated with Good manufacturing practice (GMP) failure and allergic reactions occurring at higher than expected rates reported with one particular lot of immunoglobulins.[21]

Thus, a strong biovigilance system is required to monitor the risks associated with use of biologics:

a. To collect information about risk and detect a pattern of disease transmission of AEs[4]
b. To maximize benefits and minimize the risk by educating the community[4]
c. To decrease the risk of transmission of diseases/infections by identifying the source of pathogen exposure, establishing eligibility, and deferral criteria for a donor on the basis of source of pathogen exposure[4,21]
d. To make use of data by regulatory authorities and establish guidelines and standards regarding the manufacturing and safe use of biological products[21]
e. To assure the patient safety and QOL by supplying safer products.[21]

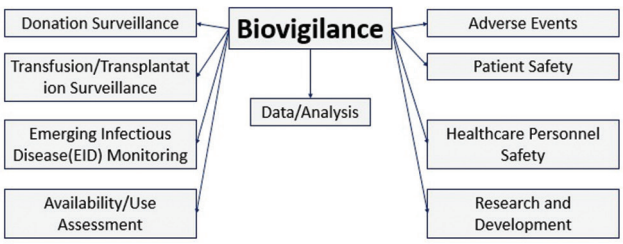

Figure 1: Overview of biovigilance

BIOVIGILANCE PROCESS

Biovigilance is the chain process, which includes the following series of events:

a. Checking for the quality of products
b. Screening and testing of the donor for various infections that are transmittable through transfusion or transplantation of biological products
c. Improvement in transfusion or transplantation processes and procedure and
d. Monitoring, identification, and resolving the risk of AEs in donors and recipients followed by further prevention of these AEs.[20]

The assessment, management, and communication of risk of AEs associated with biological products are very crucial for the improvement in the patient QOL. Absolute elimination of AEs are not possible, but these can be reduced by a thorough review of the processes involved in the development of biological products, analysis of quality of the product, and the observed outcomes in patients. Data have been collected and analyzed, and risk assessment has been performed to minimize the process errors and human errors that can affect the health of donor and biological outcomes in recipients. The possible strategies such as process improvement, implementation of standards guidelines strictly during the manufacture/transport/storage/distribution should be implemented to decrease the risk of AEs associated with biological products.[4]

THE US BIOVIGILANCE NETWORK-HISTORY AND DEVELOPMENT

Regarding biovigilance of AEs related to eye transplantation, Medical Advisory Board of Eye Bank Association of America was implemented in 1991 which was redesigned online to follow-up patient for 3–12 months for outcomes related to eye transplantation in 2005.[22] A "sentinel event reporting system" was established in 1996 for the reporting of sentinel AEs includes transfusion errors.[23,24]

Table 1: Examples of adverse events associated with the use of different biological products

Biological product category	Type of product	AEs	Reference
Tissue and organ	Musculoskeletal allograft	HIV transmission HCV transmission HLTV-1 transmission EBV, CMV, WNV, and CJD transmission	[6]
	Cornea transplantation	Graft failure in 20% cases Infectious keratitis in 11% cases Endophthalmitis in 1% cases Transplant rejection in 34% cases Other incidents in 34% cases	[9]
	Kidney transplantation	Donor cancer transmission to recipient Renal cancer in 19% cases melanoma in 17% cases lymphoma in 14% cases Lung cancer in 9% cases	[10]
		Donor-derived rabies virus transmission in two patients	[11]
	Liver transplantation	Donor-derived rabies virus transmission in two patients	[11]
	Kidney and liver transplant from common donor	Death with transmission of lymphocytic choriomeningitis virus	[12]
	Combined heart and liver transplant	Fusarial infection after 1 year of transplantation	[13]
Blood and blood products	Blood donation-related AEs	Donation-related adverse event rate was found to be 0.6% Most commonly observed donation-related adverse event was vasovagal reactions of mild intensity (approximately 70% of all donation-related adverse reactions)	[14]
	Blood transfusion-related AEs in recipients	Immediate transfusion reactions were observed in 0.19% cases Febrile nonhemolytic reactions in 37.2% recipients of red cell concentrate	[15]
Cell-based therapy	Hematopoietic stem cell transplant recipients	*Aspergillus* infection	[16]
	Human islet cell transplantation in type 1 diabetes	Bleeding required blood transfusion was observed in 10.4% case Infections in 4.1% cases Development of donor-specific antibodies in 4% cases.	[17]
Vaccination	Pertussis vaccine	Increase in pertussis cases due to insufficient potency of vaccine in China	[18]
Monoclonal antibodies	Pembrolizumab	Potential endocrine toxicity (thyrotoxicosis) in a malignant melanoma patient	[19]

WNV: West Nile virus, CMV: Cytomegalovirus, CJD: Creutzfeldt-Jakob disease, EBV: Epstein-Barr virus, HLTV-1: Human T-cell leukemia virus type 1, AEs: Adverse events

The public-private partnership between the American Association of Blood Banks (AABB) and other agencies has been established because of the impact of WNV epidemic in the USA. The task force including the representative from different organizations such as AABB, Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), USA Defense, American Red Cross (ARC), American Blood Center, Canadian Blood Services, and United Blood Services was constituted to track transfusion-related AEs in the USA. This task force has established an electronic data network in 2006 to capture information regarding WNV from each blood collector in the USA to improve the patient safety.[1] The AABB and CDC came forward with initiative to create a module of the National Healthcare Safety Network (NHSN) with the vision of improved patient safety.[25]

The "national biovigilance network" was initiated in 2006 with the aim to assure patient safety. Biovigilance network is a unique public–private partnership between DHHS, CDC, professional blood industry organizations (AABB), facilities involving in blood collection and transfusion, and organizations involved in cellular therapies, and tissue and organ transplantation.[23] The hemovigilance initiatives were implemented in 2010 with the implementation of NHSN module of CDC to assure safety relating to transfusion.[1,26,27] Tissue net is another initiative for reporting of AEs associated with tissue transplantation. The Joint Commission has prepared the standard guidelines and documents for the handling, storage, and issuance of tissue along with AABB.[28] The Center for International Blood and Marrow Transplant Research (CIBMTR) was awarded with a contract for the establishment and maintenance of Stem Cell Therapeutic Outcomes Database by Health Resources and Services Administrator. It has made mandatory for all transplant centers to submit data on all allogenic recipients on annual basis to CIBMTR, and it focused on outcomes and related AEs.[22]

The US biovigilance network has been divided into these four major system components:[23]

a. Recipient hemovigilance network
b. Donor hemovigilance network

c. Tissue and organ biovigilance network
d. Cell therapy biovigilance network.

Activities under recipient hemovigilance

To implement hemovigilance program at the national level, CDC has developed web-based surveillance system (NHSN hemovigilance module) for the determination of magnitude of transfusion-related AEs among patients and health-care personals in the USA.[26,29] Different activities that come under biovigilance has been summarized in Table 2.

Activities under donor hemovigilance

"AABB Inter-organizational Task Force" on biovigilance to track AEs relating to blood donation established the donor hemovigilance network. This network was the collaborative effort of DHHS, Armed blood services, and private organizations such as AABB and ARC and facilities involving in blood collection.[29,31]

Data collected for biovigilance network for highly prevalent infections such as Zika virus, WNV, and Chagas disease has been screened of donors by using screening tests approved by FDA, that is, nucleic acid amplification tests.[32]

Activities under tissue and organ biovigilance

Organ and tissue transplantation carries the risk of inherent disease/infection transmission in recipients and donors. Tissue and organ biovigilance network was established to promote donor and recipient safety.[32] The number of safety gaps and priorities of intervention had been identified in this workshop. A pilot system known as "Transplantation transmission sentinel network" (TTSN) was developed by "United Network for Organ Sharing" in collaboration with CDC to develop a system able to bridge safety gaps as well as fulfill the requirements identified in the workshop.[32]

The advisory committee of TTSN has identified, following five key elements for the development of prototype system for organ and tissue transplantation:

i. Registration of donor and recipient
ii. Reporting of AEs
iii. Communication of information to regulatory and public health agencies
iv. Community education.[33]

The tissue working group established by interorganizational task force meet regularly to discuss and develop ideas regarding collection and reporting of tissue and organ transplantation-related AEs in the USA.[32]

Activities under cell therapies biovigilance

Cell therapies biovigilance involves in the tracking of human cells (including stem cells), transplantation-related AEs in recipient and donors of cells and cellular components. This network is not in operation at present, and no module has been developed for reporting of cell transplantation and cellular therapies-related AEs.[32]

THE EUROPEAN HEMOVIGILANCE NETWORK

The European Hemovigilance Network (EHN) was established in 1998. This network was established with the aim to develop common structure for hemovigilance system across Europe. Initially, five countries Belgium, France, Luxembourg, the Netherlands, and Portugal come forward and joined together to work in the field of hemovigilance. Later on, other countries also joined

Table 2: Activities under biovigilance

Biovigilance activity	Activities	Reference
Recipient hemovigilance	Tracking of blood and blood products transfusion-related AEs Assure recipient and donor safety Minimization of transfusion-related morbidity and mortality Identification of blood transfusion-related infections It also helps participating facilities to develop AEs reporting methods and data analyzing methods to ensure the patient safety	[30]
Donor hemovigilance	Track AEs associated with blood donation with the aim to protect the health of donors The aggregate of this donor hemovigilance data is used to find out the pattern of blood collection-related AEs to improve donor safety This program is established for the reporting of blood collection related AEs Under this donor hemovigilance program biovigilance network for highly prevalent infections such as Zika virus, WNV, and cages disease has been established	[30]
Tissue and organ biovigilance	Registration of donor Registration of recipient Reporting of adverse event Sharing of information with regulatory authorities and public health agencies Education within the community	[30]
Cell therapy biovigilance	Established with aim of tracking of AEs relating to human cells, including stem cells collection and transplantation. Yet this network is not working	[30]

WNV: West Nile virus, AEs: Adverse events

this network either as a full member or as associate member. Denmark, Greece, Finland, Ireland, and the UK joined as full members while Switzerland, Canada, and Norway joined as associate members.[34] The European Union has developed the four directives for the safe transfusion of blood and blood products. These directives include 2002/98/EC, 2004/33/EC, 2005/61/CE, and 2005/62/CE.[35] The directive 2002/98/EC talks about quality standards and safe collection, testing, processing, storage, and distribution of blood and blood products.[36] The directive 2004/33/EC talks about eligibility criteria for donors, storage, transport, distribution, and quality control for blood and blood products.[37] The directive 2005/61/CE talks about requirements for tracking serious AEs. The directive 2005/62/CE talks about requirements for quality system for blood establishments at the community level.[35]

In 2003, the biovigilance was established in France for reporting of AEs associated with tissue and organ transplantation. The project known as **"**The European Union Standards and Training for the Inspection of Tissue Establishments" assisted the member countries regarding reporting of AEs and training of staff for the inspection of tissues, organs, and cells establishments. Directive 2004/23/EC for standards for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells was developed in March 2004.[38] The technical requirements for the donation, procurement, and testing of human tissues and cells comes under Directive 2006/17/EC, and requirements for traceability, notification of serious AEs and other aspects, including coding comes under Directive 2006/86/EC.[39,40] The availability of organs is very less in most of the EU countries and to fulfill the growing demand for organs EC highlighted the need for availability and accessibility to high quality and safe transplantation.[41]

Directive 2010/45/EU was developed in 2010 to set standards of quality and safety of human organs intended for transplantation.[41] A good regulatory framework for vaccine safety and efficacy is also established under the European Union.[42]

INTERNATIONAL HEMOVIGILANCE NETWORK

EHN was established in 1998, and it gave birth to international hemovigilance network (IHN) in 2009 with the aim to spread hemovigilance network across the world. It brings together individuals and organizations from around the world with a vision of effective hemovigilance system across the world. The mission of this network was to promote patient and donor safety worldwide by providing resources to support hemovigilance at international level. INH holds international scientific seminars and provides a forum for developing definitions and for sharing and analyzing data for benchmarking and practice improvement. IHN serves as a resource for existing hemovigilance systems and provides support in the development and establishment of new hemovigilance systems to participating countries. The symposium on hemovigilance is held annually by INH in one of the member countries.[43]

BIOVIGILANCE IN AUSTRALIA

In Australia, biovigilance comes under the Therapeutic Goods Act (TGA) 1989 and rules 1990.[44] TGA defines a biovigilance system as a system to fulfill the tasks and responsibilities associated with the detection, assessment, understanding, and prevention of AEs of biological.[44,45] TGA has established vigilance systems for collecting and evaluating information relevant to the benefit-risk balance of all therapeutic goods, including biologicals. They continually monitor the safety profile of therapeutic goods available in Australia and take appropriate action where necessary.[44]

As per TGA, Australia, every sponsor is legally responsible for meeting biovigilance requirements for their products, even if their products are the same as products belonging to other sponsors.[44,45] As per Therapeutic Goods Order No. 87, subsection 6,[1] a biological should be traceable from donor to product release.[44] To enter medicine or biological product in the Australian Register of Therapeutic Goods, it is required to submit risk management plans (RMPs) for evaluation with certain higher-risk applications.[44] RMPs must be maintained throughout the lifecycle of the product and important updates submitted to the TGA for evaluation.[45]

BIOVIGILANCE IN INDIA

In 1985, the Government of India (GOI) started the program for vaccine safety; namely, "AEs Following Immunization" (AEFI) surveillance program with the aim of promoting vaccine safety in India. The risk assessment is done by comparing the risk associated with vaccine in immunized child with the risk of disease in nonimmunized child. Despite this program, reporting has been noted to be suboptimal for AEs relating to immunization for a long time. To enhance reporting, the GOI prepared and implemented the "National AEFI Surveillance and Response Operational Guidelines" in

2005. WHO and other partners for the development of these guidelines provided the technical assistance. These guidelines were revised again, updated in 2010 and it helped in the improvement of reporting of AEFI in India. These guidelines for AEFI were proposed into two sets: Operational guidelines and standard operating procedures. These guidelines are based on the framework provided by the WHO and prepared with the help of various agencies involving in immunization program across the country, state government immunization program managers, academic institutes, subject experts, pediatricians, and officials from the office of Drugs Controller General of India.[46]

In India "hemovigilance program of India (HvPI)" has been started under the aegis of Ministry Of Health and Family Welfare by National Institute of Biologicals (NIB) under PvPI in December 10, 2012. NIB is an autonomous institute, which evaluates and assures the quality of vaccines in the country and it was chosen as the center for analysis of data regarding AEs relating to blood transfusion. Efforts have been made to improve reporting of AEs associated with blood transfusion including the development of the reporting form as well as the development of the Hemo-Vigil Software (Recipient Hemovigilance) and the Donor-Vigil Software (Donor Hemovigilance) developed by National Institute of Biologicals in conjunction with HvPI.[47]

The biopharmaceutical industry is very fast growing and enormously expanding in India. The guidelines on biosimilar were established with the aim to regulate their manufacturing as well as to assure their quality and safety. Regulatory agencies evaluate biosimilar based on their level of similarity to, rather than the exact replication of, the innovator drug.[48] Including hemovigilance across the country under the Indian Pharmacopoeia Commissions (IPCs)-PvPI, these organizations also working on herbovigilance, cosmetovigilance, and materiovigilance, which are the new emerging fields for the QOL of patients.

The department of biotechnology (DBT, Ministry of Science and Technology) in collaboration with Central Drugs Standard Control Organization (CDSCO, Ministry of Family and Health Welfare), GOI has launched guidelines regarding manufacturing and supply of biosimilar products in the year 2012. Recently, this DBT-CDSCO 2012 guideline on biosimilar was revised in the year 2016 and became effective from August 15, 2016. The move is aimed at upgrading and maintaining the quality of biosimilar products that are manufactured in India.[48]

Another significant advance is launching of Biovigilance Programme of India by NIB, in collaboration with IPC with the aim of tracking the AEs and incidences associated with the use of biologicals.

CONCLUSIONS

Biovigilance programs are currently in the developing stage. Although most countries have a nationwide hemovigilance program, biovigilance programs are absent in most countries. With the advancement of medical technologies, requirement of cell, tissue- and organ-based therapy is increasing day by day. Thus, there is a need for more targeted and stringent regulations to monitor and prevent AEs associated with the use of these products.

A well-defined nationwide biovigilance program can help assure the quality of biological products, appropriate screening and testing of the donor, improvement of the administration procedure, and establishing the eligibility criteria for the donors and recipients through biovigilance. Thus, AEs associated with transfusion or transplantation biological products may reduce.

Future epidemiological studies are required to determine the pattern of infectious diseases associated with biological products and infections to which the population is mostly exposed. After the identification of infectious, agents to which most of the population is exposed, the development of test is required for the identification of infectious agent. It is very helpful for the establishment of eligibility and deferral criteria for the donor, which is very crucial for the proper screening of donor to prevent the risk of transmission of infections associated with biological products. Biovigilance is required to evaluate the efficacy of the current manufacturing processes in clearing out the pathogens responsible for infections or infectious diseases by keeping the proper check on manufacturing processes and procedures whether they comply with GMP.

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There are no conflicts of interest.

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