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BULLETIN ON ADVERSE DRUG REACTIONS

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INDEX

From the Editor's Desk . . . . ✍

Dear Readers,

With a great a pleasure we present to you the third issue of this year. In the coming year we are working towards escalating this academic activity to a new height.

In this issue we have incorporated review articles on adverse effect due to monoclonal antibodies and biosimilars. I hope both these articles provide the readers an interesting academic information.

The case report on zidovudine induced cardiomyopathy discusses in details the risk factors, treatment and preventive strategies for the ADR. We also have a short update on newly approved monoclonal antibodies and safety alerts generated worldwide for these drugs.

Finally, I would like to thank all the clinical departments from our institute for their valued contribution to Pharmacovigilance and to the authors for contributing.

With immense pride and privilege, I would also like to thank all the members of the Department of Pharmacology for their efforts in bringing out the current issue of this publication.

Thank you,

Dr. Sudhir Pawar

ADVERSE DRUG REACTIONS ASSOCIATED WITH MONOCLONAL ANTIBODIES

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Abstract

Recently, due to advancements in the research regarding monoclonal antibodies and transition from mouse to fully humanised monoclonal antibodies have transformed the medical care and have provided a safer and targeted treatment modality to tackle some of the toughest disorders known to mankind. However, experience with TeGenero showed the possibility of catastrophic outcomes and need for radical changes in methods of how monoclonal antibodies are assessed for safety and selection of first in human dose. This review discusses the safety aspect of various commonly used monoclonal antibodies under the heading's immune reactions, infections, autoimmune disorders, cancers etc. and how our experience with monoclonal antibodies till now have shaped the regulations.

Keywords:

Biological agents, Immunogenicity, Safety, Therapeutic antibodies.

Introduction

Kohler and Milstein published their seminal manuscript on hybridoma technology in 1975, enabling mouse monoclonal antibodies to be generated. [1,2] Since then, technological advances have enabled the transition from mouse to fully human monoclonal antibodies through chimeric and humanized components, reducing the potential for immunogenic components of the mouse. [3,4] Initially, the perception towards monoclonal antibodies was that - in comparison to small molecule drugs - they could exert their pharmacologic effect with only minor safety concerns, an advantage particularly in oncology. One argument was the structural similarity to naturally occurring immunoglobulins. [5] However, experience with TGN1412 has clearly shown that even life-threatening adverse effects can very well be associated with monoclonal antibodies. This Review discusses a range of adverse effects encountered with monoclonal antibody therapy, some of which have been fatal.

Immune reactions

Despite containing elements that may be recognized as foreign by the recipient, monoclonal antibodies are generally well tolerated in humans and can therefore induce activation of immune and innate reactions. Acute reactions following infusion of monoclonal antibodies can be caused by various mechanisms, including acute anaphylactic [IgE-mediated] and anaphylactoid reactions against the monoclonal antibody, serum sickness, tumour lysis syndrome [TLS] and cytokine release syndrome [CRS]. The clinical manifestation can range from local skin reactions at the injection site, pyrexia and an influenza-like syndrome, to acute anaphylaxis and systemic inflammatory response syndrome, which could be fatal. Infusion reactions commonly occur after initial dosing, but these can be managed by recognition of risk factors, appropriate monitoring and prompt intervention. First-dose infusion reactions to some monoclonal antibodies may

combine TLS, CRS and systemic inflammatory response syndrome for example rituximab which is a chimeric CD20-specific monoclonal antibody. These initial reactions can be minimized by ensuring appropriate hydration and diuresis, premedication and cautious incremental increases in the rate of infusion. [6,7]

Acute anaphylactic and anaphylactoid reactions are commonly described for certain monoclonal antibodies such as the chimeric epidermal growth factor receptor [EGFR]-specific monoclonal antibody Cetuximab, which has been attributed to the development of IgE antibodies against galactose-?-1,3- galactose. Omalizumab which is directed against human IgE and is used in the treatment of severe allergic asthma, but it has been found to cause anaphylaxis in approximately 0.1-0.2% of patients this includes cases with delayed onset of symptoms. [8,9] The mechanisms underlying these acute reactions with Omalizumab are still poorly understood.

The immunogenicity of the foreign protein, resulting in adverse effects and loss of effectiveness, is a significant restriction in mouse monoclonal antibody therapy. Muromonab-CD3 [also referred to as Orthoclone oKT3] is a human CD3 mouse monoclonal antibody that has been used to suppress rejection of renal allograft, but can induce CRS. An acute and often extreme influenza-like syndrome may also be caused, which may be partly due to interactions with human anti-mouse antibodies. [10,11]

It has been noted that immunogenicity of a monoclonal antibody is not simply a matter of the percentage homology with human antibody, as alterations in particular amino acids at certain positions can also influence immunogenicity. Natalizumab which is a humanized monoclonal antibody against the adhesion molecule ?4 integrin, which, when used as a T-cell directed therapy for multiple sclerosis, causes severe hypersensitivity reactions in up to 1% of subjects. It can also cause mild-to-moderate infusion reactions such as urticaria or rash in about 4% of patients. These reactions generally, occur in the first 2 hours after infusion and are more common after the second or third infusion but usually less severe. Immunogenicity to Natalizumab, with persistent neutralizing antibodies, is associated with both reduced efficacy and infusion reactions in patients with multiple sclerosis. [12,13]

Serum sickness is well described in case of antisera however, monoclonal antibody therapy can also cause both anaphylaxis and serum sickness; this has been particularly noted for chimeric monoclonal antibodies. There are now methods to minimize the immunogenicity of monoclonal antibodies, as well as for the assessment of their immunogenicity, with TNF-specific monoclonal antibodies being an area of particular focus. The European Medicines Agency [EMA] has issued guidelines for the assessment of immunogenicity of biologics. [14,15] Tumour lysis syndrome is a potentially life-threatening complication that can occur early with monoclonal antibody therapy for neoplastic conditions, although this lysis is related to the desired effect of the agent. The condition has been noted with Rituximab for chronic lymphocytic leukaemia and different lymphomas. Although guidelines have been issued for the management of paediatric and adult TLS, these have attracted criticism for not being sufficiently evidence-based and the initial focus should be on preventing TLS. [16]

Infections

Infectious diseases are a well-described side effect of certain monoclonal antibodies, and they are a reflection of an acquired immunodeficiency, generally due to removal of the target ligand for that monoclonal antibody. Indeed, particular types of infections illustrate the protective function of the target ligand in the normal immune system, and provide insights into the function of this molecule to combat particular pathogens.

Reactivation of tuberculosis:

Therapy directed against the pro-inflammatory cytokine TNF? has contributed greatly to the management of severe rheumatoid arthritis and other arthritides. However, the tendency for reactivation of latent tuberculosis is a serious and limiting side effect. In a meta-analysis, TNF-specific monoclonal antibody therapy has been associated with an increased risk of serious infections and malignancies. [17]

Progressive multifocal leukoencephalopathy:

Progressive multifocal leukoencephalopathy [PML] is an often lethal, rapidly progressive demyelinating disease commonly caused by reactivation of a latent central nervous system infection with the John Cunningham polyoma virus [JCV]. Most healthy people are seropositive for JCV and its reactivation can occur after immunosuppression. Reactivation has also been reported after using Natalizumab to combat T-cell trafficking and adhesion in multiple sclerosis. [18] In November 2004, Natalizumab was approved by the US Food and Drug Administration for the treatment of relapsing-remitting multiple sclerosis, but it was suspended in February 2005 on the discovery of three cases of PML: two cases in patients with multiple sclerosis and one in a patient with Crohn's disease. Natalizumab was reintroduced in July 2006 as second-line monotherapy for multiple sclerosis with specific warnings and precautions, including the TOUCH prescribing program to minimize risk of PML. [19,20] Guidelines for patient selection and monitoring have been proposed to minimize the risk of PML, including clinical assessment, magnetic resonance imaging of the brain and cerebrospinal fluid analysis for JCV-DNA. [21] Recently, 57 cases of PML have been described after Rituximab therapy. So far, the humanized CD11a-specific monoclonal antibody Efalizumab has been associated with 4 confirmed cases of PML when used to treat patients with chronic plaque psoriasis hence, suspension of marketing authorization has been recommended by the EMA, and there has been a phased voluntary withdrawal of Efalizumab in the US. [22,23]

Platelet and thrombotic disorders

An acute, severe, self-limiting thrombocytopaenia can be caused by Infliximab [TNF?-specific], Efalizumab [CD11a-specific] and Rituximab [CD20-specific]. Abciximab is an antiplatelet glycoprotein IIb/IIIa, chimeric Fab antibody fragment that has been extensively used to treat percutaneous coronary interventions, as it blocks interactions between platelets and fibrinogen. Acute thrombocytopaenia develops after first infusion of Abciximab in about 1% of patients. Acute thrombocytopaenia occurs in more than 10% of patients after a second infusion. Thrombocytopaenia can also be delayed by 7 days, and be caused by antibodies against murine epitopes and abciximab-coated platelets. [24,25] Alemtuzumab was originally used for graft versus-

host disease following bone-marrow transplantation has also been used in the treatment of chronic lymphocytic leukaemia and during renal transplantation. More recently, Alemtuzumab has been successfully used for autoimmune diseases, especially multiple sclerosis. [26] It has been shown to cause severe multi-lineage haematopoietic toxicity involving lymphopenia, neutropenia and thrombocytopenia. [27] Bevacizumab which is a humanized monoclonal antibody against vascular endothelial growth factor [VEGF] that has been associated with arterial thromboembolic events. [28] Also a meta-analysis study showed that it increased the incidence of venous thromboembolism. [29]

Autoimmune diseases

Monoclonal Antibodies have the potential to cause various autoimmune conditions through their immunomodulatory actions, including immunosuppression, some of which are listed below.

Lupus-like syndromes and drug-related lupus:

The use of TNF-specific monoclonal antibodies for rheumatic diseases has been linked to the production of double-stranded DNA antibodies and antibodies, as well as lupus-like syndromes. The development of musculoskeletal symptoms and lupus-like syndromes is rare and sometimes subsides with the cessation of therapy. Cutaneous or systemic vasculitis, nephritis, and demyelinating syndromes are some of the other autoimmune complications. [30]

Thyroid disease:

In an initial study of 27 patients with multiple sclerosis receiving Alemtuzumab, 9 patients developed autoantibodies to the thyrotropin receptor and an autoimmune hyperthyroidism. [31]

Autoimmune colitis:

CTLA4-specific monoclonal antibodies like Ipilimumab and Tremelimumab have been found to be associated with development of enterocolitis. [32]

Cancer

Some monoclonal antibodies can contribute to tumour progression in a similar way to other immunosuppressive agents, instead of excessive acute removal of malignant cells. Association of following monoclonal antibodies with increased risk of malignancy remains controversial. However, following are some of the examples of the probable associations. [33,34,35]

- Solid cancers in patients with rheumatoid arthritis treated with TNF-specific monoclonal antibodies
- Lymphomas in patients of Inflammatory bowel disease treated with Infliximab
- Theoretical concerns over potential tumorigenicity and use of interleukin-12/23 specific monoclonal antibody

Dermatitis

The EGFR-specific monoclonal antibodies Cetuximab and Panitumumab are effective therapies for refractory metastatic colorectal cancer. These monoclonal antibodies commonly cause a skin rash on the face and upper torso, although dermatitis can present as dry skin, pruritus and erythema. The rash is generally mild to moderate, and usually occurs in the first two weeks of therapy. The dermatitis is thought to be part of the pharmacodynamic action of this agent, as EGFR is a transmembrane glycoprotein that is widely expressed on epithelial cells, and there is a correlation between presence of the rash and a positive drug response. [36] Prophylactic oral minocycline has shown some efficacy in decreasing the severity of skin reactions in the first month of Cetuximab therapy. [37]

Cardiotoxicity

Trastuzumab is a humanized monoclonal antibody directed against human ERBB2 [also known as HER2/neu] and has been used successfully in women with ERBB2-positive metastatic breast cancer. Cardiotoxicity of Trastuzumab is an on-target consequence due to blocking all downstream ERBB2 signalling and inducing MoMp, release of cytochrome c and activation of caspase, resulting in cardiac muscle cell apoptosis with reduced contractility and ventricular function. Trastuzumab also inhibits the action of neuregulin-1 [NRG1] by multiple pathways in cardiac myocytes. Trastuzumab induced cardiac dysfunction is an asymptomatic reduction in the left ventricular ejection fraction that appears to be reversible. However, this reacts well to normal medical management, if heart failure occurs. [38,39]

Cytokine storm

Various monoclonal antibodies trigger the release of a range of cytokines, causing a cytokine storm or CRS. CRS is a prominent feature in the context of therapy with CD3- specific Muromonab, CD52-specific Alemtuzumab and CD20-specific Rituximab. [40] Another popular example includes that of 2006, when the fully humanized monoclonal antibody TGN1412 - a CD28 super agonist [CD28SA] was first given to six healthy male volunteers, it triggered an immediate and severe cytokine storm characterized by prolonged cardiovascular shock and acute respiratory distress syndrome. The importance of considering the minimum expected biological impact level [MABEL] in determining the initial dose of a biologic to be used in humans was highlighted by expert groups after this incident, i.e., on the basis of the lowest dose found to be effective in any in vitro potency assay. [41]

Regulations

As an immediate response to the TGN1412 disaster, the EMA issued a guideline to identify and decrease risk with new medicinal products being studied in first-in-human clinical trials. In addition, detailed regulatory guidance is available on preclinical safety evaluation of pharmaceuticals and biologics. [42,43,44] And in combination to in vivo and in vitro models, one approach that needs greater consideration is use of micro dosing studies, with careful pharmacokinetic and pharmacodynamic evaluation in preliminary human studies. [45,46]

Conclusion

From the future perspective we need to recognize which types of risks apply to a particular monoclonal antibody and take steps to identify and minimize potential adverse effects. Through sound preclinical and clinical practice, infusion reactions can be minimized, whereas predisposition to infection can be minimized by proper monitoring and treatment selection. Preclinically, the key need is to establish and validate adequate in vitro biologics safety tests for human blood and tissues and to provide predictive CRS tests for human administration. There is a need for collaboration between scientists and physicians, pharmaceutical and biotechnology organizations, and individuals involved in the conduct and control of clinical studies to ensure the safety of participants in clinical trials. Together, these steps would help to improve the safety of monoclonal antibodies, which is vital for their expanded use in the treatment of human conditions.

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BIOSIMILARS

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Abstract

As biologic medicines lose patent protection, there are continuous efforts for developing similar versions of these costly and complex treatment with an aim of providing more affordable treatment with affordable products. That is why products known as biosimilars, are now approved worldwide and several more are expected to be introduced in the near future. This ensures that there are no clinically meaningful differences compared with respective biologics, with regard to purity, safety and efficacy. A number of biosimilars have currently been approved in oncology and other diseases and also the number is expected to rise in the near future. This review aims to provide an overview of the biosimilars used in present and their main benefits, how are they different from original biologic, how they are approved and their current roles.

Keynotes:

Biologics, Oncologic Biosimilars, Filgrastim, Reference Product.

Introduction

In recent years, biologics have increasingly been used for the treatment and palliative care of various diseases, including, but not limited to, cancer, autoimmune diseases, cardiovascular diseases and metabolic disorders. Biologics are made or derived from a biological source and are typically large complex recombinant proteins, encompassing hormones, small proteins, vaccines, fusion proteins and monoclonal antibodies. [1]

Biologics account for half of the pharmacological market in oncology; however, their main drawback is their high cost. As patents of these biologics began to expire, biosimilars were developed in order to address the existing needs and facilitate access to novel treatments for all patients. As compared with biologics, biosimilars are generally cheaper and more affordable; therefore, they have the potential to significantly reduce healthcare costs. [2]

The development of biosimilars is an attempt to reduce treatment costs. Biosimilars must be nearly identical to their reference biologics in terms of efficacy, side effect risk profile, and immunogenicity.[3]

The United States Food and Drug Administration (FDA) defines a biosimilar as "A biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product." [3]

What is difference between Biosimilars and Generic drugs?

Biosimilars and generic drugs are versions of brand name drugs and may offer more affordable treatment options to patients. Biosimilars and generics are each approved through different abbreviated pathways that avoid duplicating costly clinical trials.

For example, the active ingredients of generic drugs are the same as those of brand name drugs. In addition, the manufacturer of a generic drug must demonstrate that the generic is bioequivalent to the brand name drug.

By contrast, biosimilar manufacturers must demonstrate that the biosimilar is highly similar to the reference product, except for minor differences in clinically inactive components. Biosimilar manufacturers must also demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety and effectiveness. [4,5]

How are Biosimilars approved?

All FDA-approved biological products, including reference products and biosimilar products, undergo a rigorous evaluation so that patients can be assured of the efficacy, safety, and quality of these products. [4]

A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared. A reference product is approved in a "standalone" application that must contain all data and information necessary to demonstrate its safety and effectiveness. This will also include clinical trials for the disease indications being sought by the manufacturer.

A biosimilar is highly similar to, and has no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) from, an existing FDA-approved reference product.

The manufacturer of a proposed biosimilar product generates an array of data comparing the proposed product to the FDA-approved reference product in order to demonstrate biosimilarity. The comparative data are generated and evaluated in a stepwise fashion that begins with a foundation of detailed analytical (structural and functional) characterization and comparison of the products, moving on to animal studies if necessary and then to comparative clinical studies. [6]

Once manufacturer that shows if its proposed biosimilar product is highly similar to and has no clinically meaningful difference from the FDA-approved reference product.

Biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients.[6]

A biosimilar product application must include data demonstrating biosimilarity to the reference product. This usually includes data from

- Analytical studies demonstrating that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components;
- Animal studies, including an assessment of toxicity; and
- A clinical study or studies sufficient to demonstrate safety, purity, and potency of the proposed biosimilar product in one or more of the indications for which the reference product is licensed. This typically

includes assessing immunogenicity, pharmacokinetics (PK), and, in some cases, pharmacodynamics (PD) and may also include a comparative clinical study [6,7]

How are Biosimilars are developed?

The development of biologics involves multiple levels of intricate, highly controlled manufacturing processes, combined with preclinical structural, functional, and biological assessments, as well as clinical efficacy and safety, including immunogenicity, analyses [8].

In addition, to ensure a high degree of similarity, a biosimilar must undergo a comparability exercise at every step of its development, as outlined by regulatory agencies, to demonstrate that potential differences from the reference product are not clinically meaningful with regard to quality, safety, and efficacy (European Medicines Agency [EMA]) or safety, purity, and potency (US Food and Drug Administration [FDA]).

At the foundation of the biosimilar development process lays the establishment of a high degree of structural similarity with its reference product. State-of-the-art technologies must be employed to demonstrate a high degree of structural and functional similarity.

Finally, clinical pharmacokinetic and pharmacodynamic as well as clinical efficacy and safety similarity must be confirmed between biosimilar and originator. Regulators, including the FDA and the EMA consider the totality of the evidence from this comprehensive step-wise comparative similarity exercise in its determination of biosimilarity for licensing.[12]

The world upside down

Biosimilars follow a step-wise development

- **Quality comparability** is essential and involves comprehensive characterisation and comparison of physicochemical and biological properties; the degree of similarity demonstrated at this level might determine the amount of additional evidence that needs to be generated at later stages.
- Pre-clinical (functional) comparability

  Offers reassurance on similar effects and involves functional in vitro assays to define and compare the mode of action:-

  - **In vitro studies**

    Are always required and normally cover most functional aspects. It is essential to determine the level of concern depending on quantitative/ qualitative differences in critical quality attributes.

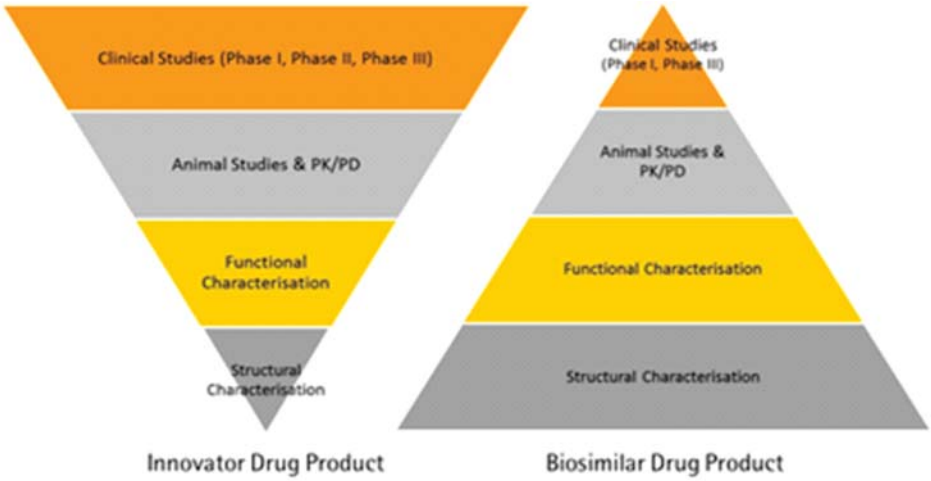
  - **In vivo PK (pharmacokinetics)/PD (pharmacodynamics) and/or safety studies**

    May be necessary in case of e.g., a new expression system

- **Clinical comparability**

  Involves testing in a sensitive population and dose at a sensitive time point using an appropriate statistical

model and testing approach; usually the details for phase III conduct are agreed upfront with the health authority of the region intended for registration.[9]



How Are Biosimilars Named?

Unlike generic medication, which can have the same chemical name as the brand name, biosimilars must include 4 lowercase letters after the name of the medication. For example, the biosimilar for the reference product filgrastim is called filgrastim-sndz. The biosimilar and the reference medication always have the same active ingredient. The addition of the 4 lowercase letters lets you know that the medication is a biosimilar.[4]

Challenges associated with the development of biosimilars

That is, biosimilar developers must not only demonstrate, through the use of the most relevant state of- the-art methods that their products maintain consistent quality manufacturing, but also are sufficiently similar to the reference product [8]. Because these companies must reverse engineer the product to develop a process that can produce a highly-similar product, the biosimilar will not have the exact characteristics of the reference product. These variations may affect glycosylation and other post-translational modifications, heterogeneity parameters such as C-terminal lysine, orproduct-related substances and impurities.[11]

Are biosimilars approved for all the same indications as the reference product?

Biosimilar products may be approved for all or a subset of the same indications as the reference product. Biosimilars may have fewer indications than the reference product if, for example, a reference product has unexpired exclusivity for an indication that prevents other manufacturers from obtaining approval for that particular indication. Health care prescribers should review the specific product labeling (prescribing information) and approved indications to determine the most appropriate product for their patient.[5]

ASCO has developed this statement to offer guidance in the following areas:

(1) Naming, Labelling, And Other Regulatory Considerations,

(2) Safety and Efficacy of Biosimilars,

(3) Interchangeability, Switching, And Substitution,

(4) Value of Biosimilars, And

(5) Prescriber and Patient Education.

- *Naming, Labelling, And Other Regulatory Considerations,*

  The naming and labelling of biosimilars, considered together, will help to ensure that oncologists, pharmacists, and other providers have all the necessary information to ensure they are using their chosen therapy as intended.

- *Safety and Efficacy of Biosimilars*

  Sustained post market evidence development is necessary to enhance patient and provider confidence in biosimilars and to supplement the evidence supporting the safe and effective use of biosimilar products.

- *Interchangeability, Switching, And Substitution,*

  The interchangeability of a product is determined at the federal level after FDA review; however, substitution will be regulated at the state level. As individual states work to regulate the use of biosimilars, in accordance with the FDA designation, oncologists and patients must be aware of the regulations, authorities, and responsibilities that may affect their treatment choices.

- *Value of Biosimilars,*

  Oncologists recognize the effect of cost and reimbursement in making treatment decisions. Biosimilars provide an opportunity to both obtain desired outcomes and manage the cost of care for patients with cancer. Coverage and reimbursement policies vary by payer, patient, and setting.

- *Prescriber and Patient Education.*

  Oncologists recognize the effect of cost and reimbursement in making treatment decisions. Biosimilars provide an opportunity to both obtain desired outcomes and manage the cost of care for patients with cancer. Coverage and reimbursement policies vary by payer, patient, and setting Oncologists recognize the effect of cost and reimbursement in making treatment decisions. Biosimilars provide an opportunity to both obtain desired outcomes and manage the cost of care for patients with cancer. Coverage and reimbursement policies vary by payer, patient, and setting. [10]

Where can you find more information about biosimilar products?

FDA's "Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations," known as the "Purple Book," is an online resource for health care professionals and patients to locate information about approved biological products. The Purple Book provides information

about whether a biological product is a reference product, biosimilar, or interchangeable product. [4,13]

Approved Biosimilars in conditions:[3]

Condition	Reference biologic	Approved Biosimilar
Crohn's disease	Infliximab (anti-TNF?) Adalimumab (anti-TNF?)	Remsima, Inflectra, Renflexis, Flixabi Amjevita, Cyltezo
Ulcerative colitis	Infliximab (anti-TNF?)	Remsima, Inflectra, Renflexis, Flixabi
	Adalimumab (anti-TNF?)	Amjevita, Cyltezo
Colorectal cancer	Bevacizumab (anti-VEGF)	Mvasi
Gastric cancer	Trastuzumab (anti-HER2/neu)	Ogivri

Approved Biosimilars in oncology:

Reference biologic	Active substance	Approved Biosimilar
Eprex/Erypo	Epoetin-alpha	Binocrit
Neupogen	Filgrastim	Ratiograstim,Tevagrastim,Biograstim
MabThera	Rituximab	Truxima, Riximyo, Rixathon
Neulasta	Pegfilgrastim	Pelgraz,Udenyca, Fulphila,Pelmeg

Conclusion

Biologics are widely used therapeutic agents in the treatment and palliative care of cancer. However, due to their high cost, crises in healthcare spending worldwide and the expiration of biologics patents, biosimilars have come to the market.Biosimilars are more affordable drugs, but with a similar safety and toxicity profile and no clinically meaningful differences compared with their reference biologics. Therefore, biosimilars enable a reduction in healthcare costs and increase a patients' access to novel treatment options regulation frameworks and close post?marketing surveillance of licensed biosimilars are required to ensure that these new drugs are safe and effective in the real-world setting.

As more biosimilars become available, the need to improve awareness and understanding of these therapeutic alternatives among clinicians and caregivers will continue to increase. Their adoption in clinical practice will, however, require an increased understanding of what they are, how they are developed, how they are approved and how they can be used in practice. Education regarding their safe use also becomes important and will be a key factor in assuring safe, cost-effective treatments for our patients.

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ZIDOVUDINE INDUCED DILATED CARDIOMYOPATHY

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Abstract

Zidovudine also known as Azidothymidine(AZT) is an anti-retroviral used to prevent and treat HIV/ AIDS. It can cause adverse effects ranging from fatigue, malaise, myalgia, nausea, anorexia, headache, insomnia to serious adverse effects like haematological effects, hepatotoxicity, cardiomyopathy, and myopathy. A case of HIV in a 14 year old female treated with ZLE (Zidovudine + Lamivudine + Efavirenz) regimen who developed dilated cardiomyopathy is reported here. According to the WHO UMC causality assessment scale, the association of dilated cardiomyopathy is a possible adverse drug reaction due to zidovudine.

Introduction

Zidovudine (3-azido-3 -deoxythymidine), also referred to as azidothymidine (AZT), is a nucleoside reverse transcriptase inhibitor. It has a potent activity against a broad spectrum of retroviruses, including HIV-1, HIV-2, and HTLVs I and II. Zidovudine is FDA-approved for the treatment of adults and children with HIV infection and for preventing mother-to-child transmission; it also was previously recommended for postexposure prophylaxis in HIV-exposed healthcare workers.[1] AZT has also been used in the treatment of cancer.[2]

Being a synthetic thymidine analogue compound, AZT undergoes intracellular triphosphorylation and inhibits viral replication by incorporating into the viral DNA strand, thus impeding the viral RNA-dependant DNA polymerase, also known as reverse transcriptase. Hence AZT has been used in the treatment of AIDS as an integral component of highly active antiretroviral therapy. Most malignant cancers express telomerase, which has reverse transcriptase activity, and are therefore prone to the inhibitory effects of AZT. Hence AZT has been used in the treatment of cancer as well.[2]

Clinical effectiveness of AZT is constrained due to its association with increased adverse effects during chronic therapy at high doses. Included among the common adverse effects are haematological effects, such as anaemia and neutropenia, hepatotoxicity, cardiomyopathy, and myopathy.[3] Myopathy is associated with depletion of mitochondrial DNA, most likely as a consequence of inhibition of DNA polymerase-? by Zidovudine-triphosphate.[1] . Although it is known that myopathy is present in advanced HIV, it is important to acknowledge the association of myopathy with AZT therapy, including reports of the association at a rate around 17%.[3] Marked improvement or resolve of symptoms are noted in range of 18-100% of patients of Myopathy with AZT therapy when the medication was discontinued.[4]

Here we present a case of Zidovudine induced dilated Cardiomyopathy in a 14yr old female who was a known case of HIV.

Case History

A 14 year old female who was a known case of HIV was brought to our hospital with Grade-III breathlessness, puffiness of face and oedema of both the legs. 3 years ago she was diagnosed as HIV seropositive and she was started on ZLE (Zidovudine + Lamivudine + Efavirenz) regimen. 6months ago. Isoniazid was added to ZLE regimen for prophylaxis against TB. After taking these medications for 2 months, she started having few episodes of vomiting and breathlessness; she was treated on symptomatic basis at PHC level. Over next 4 months, she had multiple episodes of vomiting and breathlessness, and she developed puffiness of face and oedema in both the legs. With above mentioned complaints, she was brought to our hospital. She was admitted. Chest X-ray showed enlarged heart, pulmonary oedema, and interstitial markings. ECG showed sinus tachycardia and nonspecific ST-T changes. An echocardiogram showed left ventricular enlargement, diffuse left ventricular hypokinesia and a 15%-20% left ventricular ejection fraction. She was diagnosed as case of Dilated Cardiomyopathy.

Tab Zidovudine was immediately stopped. After 3 days, she was started on TLE (Tenofovir + Lamivudine + Efavirenz) regimen. After one week, the swelling over her face and legs started to subside.

As per the WHO seriousness criteria, the reaction was serious as it was the reason for hospital admission. The causality of this reaction as per the WHO UMC causality assessment scale was "Possible" as de-challenge was positive, re-challenge with Zidovudine was not done and Dilated Cardiomyopathy could have been caused by the disease itself i,e, HIV. According to the Modified Schumock & Thornton Preventability Scale, the occurrence of this reaction was not preventable. According to the Modified Hartwig & Siegel severity assessment scale, severity of this reaction was moderate as this reaction was the reason for admission.

Discussion

Cardiac involvement in acquired immunodeficiency syndrome (AIDS) is an important problem. Among cardiac complications in the course of human immunodeficiency virus (HIV) infection, dilated cardiomyopathy (congestive cardiomyopathy) has been documented clinically [5-7] and pathologically [8-10]. Dilated cardiomyopathy in AIDS may have diverse etiologies, including sequelae of myocarditis, myocyte damage from opportunistic myocardial infection, toxicity of AIDS chemotherapeutic agents, and, possibly, infection of the heart with HIV [11,12]. The annual incidence of HIV-induced Cardiomyopathy in 2003, prior to the introduction of HAART was 15.9 per 1,000 individuals [34], and rose significantly to 176 per 1000 in 2014 after the introduction of HAART [29]. Individual antiretroviral drugs (zidovudine, didanosine or zalcitabine) have also been implicated as a possible cause of Cardiomyopathy in HIV-positive patients [30-33].

The association between AZT use and the development of cardiomyopathy has been suggested from animal models [11,13,14] In rats given AZT, ultrastructural changes in cardiac mitochondria, including increased mitochondrial size, fracture and disruption of cristae, and electron-dense deposits in the matrices,

have been noted [11,13]. Herskowitz and his colleagues reported a series of AIDS patients who received AZT (or other dideoxynucleosides) in high doses. These patients developed reversible congestive heart failure (with presumed dilated cardiomyopathy) after being treated with these agents. They improved clinically with discontinuation of dideoxynucleoside therapy [15]. Frerichs et al. reported the first adult case of cardiomyopathy caused by a zidovudine-containing therapeutic regimen [16].

This case of dilated cardiomyopathy was probably caused by zidovudine. The reasons for suspecting that zidovudine was the cause of the cardiac findings are as follows: (1) the clinical symptoms appeared after the commencement of HAART that included zidovudine, (2) the clinical signs and symptoms started improving after discontinuation of the zidovudine-containing HAART regimen, and (3) cardiac function remained normal after the introduction of new HAART regimen containing Tenofovir, Lamivudine and Efavirenz. Therefore, zidovudine seemed to have played a key role in the pathogenesis of this case.

The association of cardiomyopathy with zidovudine in adults is still unclear. The mechanism of zidovudine-induced cardiomyopathy is thought to be mitochondrial toxicity caused by zidovudine, made evident by depletion of mitochondrial DNA levels [17]. Data suggest that the mechanism of mitochondrial toxicity due to AZT administration may be caused from mtDNA depletion, mitochondrial oxidative stress, reduced content of L -carnitine, and other mechanisms such as apoptosis.

The AZT-induced dysfunction of mitochondria is caused from the reduction of mtDNA content.[4,18,19]. AZT-induced mtDNA depletion occurs due to inhibition of DNA polymerase ? and due to depletion of the mitochondrial pool of TTP (thymidine triphosphate). The depletion of mtDNA leads to dysfunctional complexes of the electron transport chain, thereby affecting oxidative phosphorylation and ATP production. Aerobic ATP production falls short of the minimum energy requirements necessary to maintain normal tissue and organ function, which leads to dysfunction. . Furthermore, anaerobic glycolysis takes over to compensate for minimal energy, leading to a buildup of lactic acid [20,21] Yamaguchi et al. reported early cytotoxic effects of AZT, and showed AZT exposure in human lymphoid cells resulted in a decrease in ATP concentration and depletion of glutathione [22]. Depletion of glutathione leads to an increase in reactive oxygen species (ROS) production. This oxidative stress can damage and alter the functions of DNA, proteins, and lipids; thus, leading to mitochondrial and cellular dysfunction. L -Carnitine, also known as levocarnitine, assists in the proper metabolism of long-chain fatty acids to energy by promoting their transport from the cytosol into the mitochondria for entry into ?-oxidation [3]. Data show that AZT causes a reduction in cellular levels of L -carnitine [23,24]. It leads to accumulation of lipid droplets in the cytoplasm of muscle cells. AZT reduces the transport of L -carnitine across the plasma membrane. AZT acts as a non-competitive inhibitor of the sodium-dependent transport of L -carnitine [3]. Apoptosis is a cell suicide program that is highly regulated and executed via activation of specific signalling pathways. AZT induced Mitochondrial dysfunction, mtDNA mutations and depletion, oxidative stress, and accumulation of cellular fatty acids have all been shown to induce apoptosis in a variety of cell types [25-28].

In HIV-infected patients receiving HAART therapy, diagnosis of CM is based on evidence of cardiac

dysfunction. Cardiac dysfunction is diagnosed based on the presence of ventricular diastolic or systolic dimensions ? 2 standard deviations above the mean for body surface area or abnormal fractional shortening index ? 2 standard deviations below the mean [35]

Conclusion

AZT has been an integral component of highly active antiretroviral therapy. Several reports have indicated that zidovudine can induce cardiomyopathy. AZT withdrawal should be considered in any patient in whom cardiomyopathy develops. If the cardiomyopathy is a manifestation of HIV infection and not a result of AZT use, then a change in therapy may be warranted on the basis of progression of HIV disease. Regardless of the cause of cardiac disease, we believe that it is important to monitor the cardiac status of HIV-infected patients with serial echocardiograms. The risk/benefit ratio of continuing AZT therapy must be carefully weighed in each patient.

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REGULATORY UPDATE AND MEDICAL NEWS

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FDA Drug Safety Podcast: FDA warns that symptoms of a serious condition affecting the blood cells are not being recognized with the leukemia medicine Enasidenib

On November 29, 2018 FDA has warned that signs and symptoms of a life-threatening side effect called differentiation syndrome are not being recognized in patients receiving the acute myeloid leukemia medicine enasidenib.

Health care professionals should describe to patients the symptoms of differentiation syndrome listed in the Medication Guide when starting enasidenib and at follow-up visits to their health care professional if such symptoms occur. Differentiation syndrome has occurred as early as 10 days and up to 5 months after starting the medicine. If patients experience unexplained respiratory distress or other symptoms, consider a diagnosis of differentiation syndrome and treat promptly with oral or intravenous corticosteroids.

Enasidenib was approved in August 2017 to treat patients with acute myeloid leukemia or AML with a specific genetic mutation called isocitrate dehydrogenase (IDH-2) whose disease has recurred or not improved after treatment with other chemotherapy medicines.

In the clinical trial conducted for enasidenib's approval, at least 14 % of patients experienced differentiation syndrome. The manufacturer's safety report, for the period of May 1 to July 31 of 2018, reported five cases of death associated with differentiation syndrome in patients taking enasidenib. Ivosidenib which is another recently approved drug for AML with the specific genetic mutation called isocitrate dehydrogenase or IDH-1 also carries a risk of differentiation syndrome.

Reference:FDA Drug Safety Podcast: FDA warns that symptoms of a serious condition affecting the blood cells are not being recognized with the leukemia medicine enasidenib [Internet].[Cited in Jan 2021]. Available from: https:www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts

FDA Drug Safety Podcast: FDA warns about rare but serious risks of stroke and blood vessel wall tears with multiple sclerosis drug alemtuzumab

November 29, 2018 FDA has warned that rare but serious cases of stroke and tears in the lining of arteries in the head and neck have occurred in patients with multiple sclerosis or MS shortly after they received alemtuzumab. These problems can lead to permanent disability and even death. As a result, we have added a new warning about these risks to the prescribing information in the drug label and to the patient Medication Guide. We have also added the risk of stroke to the existing Boxed Warning, FDA's most prominent warning.

Alemtuzumab is also approved in May 2001 to treat B-cell chronic lymphocytic leukemia. The Health care

professionals should advise patients at every alemtuzumab infusion to seek immediate emergency medical attention if they experience symptoms of ischemic or hemorrhagic stroke or cervicocephalic arterial dissection. The diagnosis is often complicated because early symptoms such as headache and neck pain are not specific. Promptly evaluate patients who complain of symptoms consistent with these conditions.

Since its approval in 2014 to treat relapsing forms of MS, FDA has identified 13 worldwide cases of ischemic and hemorrhagic stroke or arterial dissection occurring shortly after the patient received Alemtuzumab. This number includes only reports submitted to FDA. Twelve of these cases reported symptoms within 1 day of receiving Alemtuzumab and one reported symptom occurring 3 days after treatment

Reference: FDA Drug Safety Podcast: FDA warns about rare but serious risks of stroke and blood vessel wall tears with multiple sclerosis drug alemtuzumab [Internet].[Cited in Jan 2021]. Available from:https:www.fda.gov/Drugs/DrugSafety/DrugSafetypodcast

Bevacizumab: Risk of artery dissection

The Japan's Ministry of Health, Labor and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for bevacizumab should be revised to include artery dissection as an adverse drug reaction. Bevacizumab is indicated to treat several conditions such as incurable, unresectable advanced/recurrent colorectal cancer and malignant glioma.

A total of seven cases involving artery dissection in patients with bevacizumab have been reported in Japan during the previous three years, including one case for which a causal relationship between the drug and event was deemed reasonably possible. Two mortalities have been reported among the seven cases. A causal relationship could not be established for either cases. The MHLW and PMDA have concluded that revision of the package insert was necessary.

Reference: Advera Health Analytics I. Thromboembolic Adverse Events and JAK Inhibitors [Internet]. Info.adverahealth.com. 2021 [cited 1 February 2021]. Available from: https:// info.adverahealth.com/thromboembolic-adverse-events-and-jak-inhibitors

Ruxolitinib, Tofacitinib: Risk of blood clots in the deep veins

Health Canada has announced that it had worked with the manufacturer for tofacitinib to update the product safety information to include the serious risk of blood clots in the veins and will also work with the manufacturer for ruxolitinib to update the product safety information to include the risk of thromboembolic events.

Tofacitinib is used for the treatment of inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis and ulcerative colitis. Ruxolitinib is used for the treatment of certain rare blood cancers, such as primary myelofibrosis and polycythemia vera.

Health Canada conducted a safety review and found that an ongoing safety study for tofacitinib showed an increased risk of blood clots in the lungs and death. A review of an additional 51 cases (eight Canadian and

43 international) of thromboembolic events in people taking tofacitinib showed that 38 were possibly linked to tofacitinib.

A further assessment of eight Canadian cases of thromboembolic events in patients taking ruxolitinib found that three cases showed a possible link to ruxolitinib. Health Canada concluded that there is a link between the risk of thromboembolic events and the use of tofacitinib or ruxolitinib.

Reference: Advera Health Analytics I. Thromboembolic Adverse Events and JAK Inhibitors [Internet]. Info.adverahealth.com. 2021 [cited 1 February 2021]. Available from: https://info.adverahealth.com/thromboembolic-adverse-events-and-jak-inhibitors

Alemtuzumab: Updated restrictions and strengthened monitoring

Products Regulatory Agency (MHRA) has announced that an EU review recommended a revised indication, additional contraindications and strengthened monitoring for alemtuzumab due to the risk of cardiovascular events, thrombocytopenia and immune-mediated reactions.

Alemtuzumab is a monoclonal antibody and is indicated for the treatment of adults with relapsing-remitting multiple sclerosis. The review concluded that serious cardiovascular reactions can rarely occur within one to three days of treatment. However unpredictable and potentially fatal immune-mediated reactions can occur within months and up to at least four years post-treatment. This included Epstein-Barr virus reactivation.

Alemtuzumab should only be used as a single disease-modifying therapy in adults with specific conditions. Alemtuzumab is contraindicated in patients with severe active infection until complete resolution, those with a history of stroke and a history of angina.

Patients should only be administered alemtuzumab in a hospital with ready access to intensive care facilities and should be monitored closely for cardiovascular reactions and non-immune thrombocytopenia.

Reference: Alemtuzumab: updated restrictions and strengthened monitoring requirements following review of serious cardiovascular and immune-mediated reactions [Internet]. GOV.UK. 2021 [cited February 2021]. Available from: https://www.gov.uk/drug-safety-update/lemtrada-alemtuzumab-updated-restrictions-and-strengthened-monitoring-requirements-following-review-of-serious-cardiovascular-and-immune-mediated-reactions.

NEW DRUG APPROVALS- MONOCLONAL ANTIBODIES

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Monoclonal antibodies (mAb) are important group of drugs used in biomedical research, in diagnosis of diseases, and in treatment of diseases such as infections and various cancers. They were first generated in mice in 1975 using a hybridoma technique. Monoclonal antibodies are laboratory produced antibodies designed to recognise and bind to specific receptors found on the surface of cells.(1) These antibodies are produced by cell lines or clones obtained from animals that have been immunized with the substance that is the subject of study. The cell lines are produced by fusing B cells from the immunized animal with myeloma cells.

In 1986, OKT3, the first antibody derived from mouse hybridoma, was approved by the United States Food and Drug Administration (FDA) for use in patients to prevent transplant rejections. In 2002, 'Adalimumab' became the first human mAb to be approved by the US Food and Drug Administration (FDA) for rheumatoid arthritis. (2)

Monoclonal antibodies currently make up a third of all new introduced drugs. Some of their strongest impact has been in the cancer field. One of the main advantages of mAb is that they specifically target cancer cells while avoiding healthy cells. MABs have not only brought major changes to the treatment and outlook of cancer, but also to a range of chronic inflammatory and autoimmune disorders. They not only relieve symptoms but also target and disrupt their cause. (3)

Few of the recently approved Monoclonal antibodies are-

1. Ansuvimab

Ansuvimab is a human IgG1 monoclonal antibody approved On December 21, 2020, by, the US Drug and Food Administration. It was granted an Orphan Drug designation.(4)The safety and efficacy of Ansuvimab were evaluated in the multi-centre, open-label, randomized controlled PALM trial. (Pamoja Tulinde Maisha ["Together Save Lives"] in the Kiswahili language)

MOA- There is direct blockage of Ebola virus (EBOV) endolysosome escape and antibody-dependent cellular cytotoxicity (ADCC) mediated killing of EBOV-infected cells. Ansuvimab binds and neutralizes the virus.

Indication- Treatment of Zaire ebolavirus infection in adult and pediatric patients, including neonates born to a mother who tests positive for Zaire ebolavirus by RT-PCR.

Side-effect- The most common symptoms experienced while receiving Ansuvimab include: fever, tachycardia, diarrhoea, vomiting, hypotension, tachypnoea and chills.

2. Margetuximab

Margextuximab was granted FDA approval on December 16, 2020. It is a Fc engineered HER2-directed

monoclonal antibody. Efficacy was evaluated in SOPHIA (Margetuximab plus Chemotherapy vs Trastuzumab plus Chemotherapy in the Treatment of HER2+ Metastatic Breast Cancer) a randomized, multicenter, open-label trial.(5,6)

MOA- Margetuximab binds to the extracellular domain of the human epidermal growth receptor protein (HER2). Upon binding to HER2-expressing tumor cells, Margetuximab inhibits tumor cell proliferation, reduces shedding of the HER2 extracellular domain and mediates antibody-dependent cellular cytotoxicity (ADCC).

Indication- Adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

Side-effect- Increased creatinine, fatigue/asthenia, decreased haemoglobin, decreased leukocytes, decreased neutrophils, nausea, increased activated partial thromboplastin time (aPTT), increased ALT, decreased lymphocytes, increased lipase and diarrhea.

3. Naxitamab

Naxitamab, is an IgG1 monoclonal antibody directed against the oncofetal differentiation antigen GD2 disialoganglioside.(7)

MOA- Naxitamab binds to GD2 on the surface of neuroblastoma cells and induces both complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC), the latter of which is enhanced by co-administration with GM-CSF.

Indication- treatment of high-risk relapsed/refractory neuroblastoma of the bone or bone marrow.

Side-effects- Pain, infusion-related reaction, tachycardia, vomiting, cough, nausea, diarrhea, increased ALT, decreased Magnesium, decreased appetite, increased AST, decreased phosphate and hypertension.

4. Satralizumab

Satralizumab, is a humanized monoclonal antibody. (8)

MOA- Satralizumab is a humanized IgG2 monoclonal antibody that regulates inflammation by inhibiting the interleukin-6 (IL-6) receptor, a key mediator of the immune response.

It binds to soluble and membrane-bound human interleukin-6 (IL-6) receptors and thereby prevents IL-6-mediated signal transmission through these receptors

Indication- It is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adults with a particular antibody - people who are anti-aquaporin-4 or AQP4 antibody-positive. NMOSD, a rare autoimmune inflammatory disorder of the central nervous system (CNS) involving demyelinating lesions in the optic nerve, spinal cord, brainstem, and cerebrum.(9)

Side-effects- Common cold (nasopharyngitis), headache, upper respiratory tract infection, inflammation of the lining of the stomach, rash, joint pain, extremity pain, fatigue and nausea.

5. Belantamab

Belantamab mafodotin, or GSK2857916, is an afucosylated monoclonal antibody.

MOA-It targets B cell maturation antigen (BCMA) conjugated to the microtubule disrupter monomethyl auristatin-F (MMAF). Afucosylation of the Fc region of monoclonal antibodies enhances binding to the Fc region, which enhances antibody dependant cell mediated cytoxicity.

Indication

Belantamab mafodotin is indicated in the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.(10)

Side effects- Data regarding overdose is not readily available. However, keratopathy was seen in 71% of patients, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue.

6. Tafasitamab

Tafasitamab is a humanized Fc-modified cytolytic CD19 antibody (11)

MOA- Tafasitamab is a CD19-directed cytolytic monoclonal antibody that, upon binding and blocking the activity of CD19, causes lysis of B-cells. This process is mediated through both direct apoptosis and immune-mediated effector mechanisms, such as antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).

Indication- Tafasitamab, in combination with lenalidomide, is indicated for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

Side effects- Tiredness, diarrhea, nausea, vomiting, loss of appetite, back pain, or muscle spasms.

7. Inebilizumab

Inebilizumab is a monoclonal antibody approved in June 2020.(12)

MOA -It is humanized mAb that binds to and depletes CD19+ B cells including plasma blasts and plasma cells.

Indication- It is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adults with a particular antibody (patients who are anti-aquaporin-4 or AQP4 antibody positive).(13)

Side-effects- The label for Inebilizumab includes a warning for infusion reactions, potential depletion of certain proteins (hypogammaglobulinemia), and potential increased risk of infection - including Progressive

Multifocal Leukoencephalopathy (PML), and potential reactivation of hepatitis B and tuberculosis. The most common adverse reactions are urinary tract infection, headache, joint pain (arthralgia), nausea and back pain.

8. Sacituzumab

Sacituzumab is a Trop-2-directed antibody and topoisomerase inhibitor drug conjugate.

MOA- Sacituzumab is an antibody-drug conjugate (ADC) targeting TROP-2-expressing cancer cells to induce DNA-damage-mediated cell death.

Indication- It is indicated for adult patients with metastatic triple-negative breast cancer (mTNBC) who have undergone two or more prior therapies for metastatic disease.(14)

Side-effects- Patients receiving an overdose are at an increased risk of severe adverse effects such as neutropenia, diarrhoea, hypersensitivity, nausea/vomiting, and other systemic effects related to cytotoxic drugs.

9. Isatuximab

It is humanized, IgG1-derived monoclonal antibody (mAb) produced from a Chinese hamster ovary (CHO) cell line (15).

MOA- Isatuximab is targeted against CD38 proteins. This results in direct apoptosis of the affected cell and activation of immune mechanisms including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC), all of which result in potent anti-tumour activity.

Indication- It is indicated for the treatment of multiple myeloma in adults who have received at least two prior therapies including Lenalidomide and a proteasome inhibitor.

Side effect- Severe or life-threatening low white blood cell counts, diarrhea, nausea and vomiting, low red blood cell counts, feeling tired, hair loss, constipation, rash, decreased appetite

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MATCH THE ADVERSE EFFECT WITH THE DRUG

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1	Muromonab-CD3	A	To treat SJIA (Systemic juvenile idiopathic arthritis)
2	Adalimumab	B	PEGylated humanized antibody
3	Abciximab	C	Migraine
4	Trastuzumab	D	Treatment Of asthma
5	Alacizumab	E	Used to treat psoriasis and causes pharyngitis
6	Nofetumomab	F	Infusion reactions and progressive multifocal encephalopathy
7	Rozrolimupab	G	Neutralizes clostridium difficile toxin
8	Benralizumab	H	Targets TNF alpha
9	Rituximab	I	Human Polyclonal antibody
10	Belimumab	J	Merpentan links it to technitium99m
11	Alefacept	K	Thyroid Dysfunction
12	Canakinumab	L	Platelet aggregation inhibitor
13	Bezlotoxumab	M	Pain around eyes & cheekbones
14	Alemtuzumab	N	Breast cancer medication
15	Omalizumab	O	First monoclonal antibody approved for clinical use in humans

Answers : 1-O; 2-H; 3-L; 4-N; 5-B; 6-J; 7-J; 8-D; 9-F; 10-C; 11-E; 12-A; 13-G; 14-K; 15-M

We would like to request all the departments to contribute in ADR reporting.

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