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Review Article

Protocols for use of biologics in oral diseases

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ABSTRACT

Biologics are used in the treatment of immune-mediated diseases with the aim of modulating lymphocytes or cytokines. They can be categorized broadly into three categories: Tumor necrosis factor-alpha inhibitors, lymphocyte modulators, and interleukin inhibitors. Guidelines for the development of biologics include validations of various steps in development, standard guidelines, regulatory guidelines, manufacturing guidelines, and analytical tests. Hence, in this article, the guidelines and key aspects of guidelines in the use of biologics in oral diseases are presented.

Keywords: Biologics, cytokines, guidelines, lymphocytes, tumor necrosis factor-alpha, interleukin

Introduction

Biologics are an innovative treatment method aimed at tumor necrosis factor-alpha (TNF-α) inhibitors, interleukin (IL) inhibitors, and lymphocyte modulators. They have several potential applications in oral diseases and are increasingly used in treating patient with only refractory forms of inflammatory immune-mediated diseases.[1-3] Biologics are generated by recombinant technology and comprises a large number of monoclonal antibodies and fusion proteins that target specific proinflammatory pathways. Guidelines for the use of biologic in licensed indications include use of biologics in off-label situations, eligibility for use, adverse effects, infection control, and their relevance to oral diseases.[1] Regulatory guidelines for the development of biologics include validations of various steps in development, standard guidelines, manufacturing guidelines, and analytical tests. Biologics can be used therapeutically in patients who have no alternate approach whoever is not used widely due to its high economic cost.[2]

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General Guidelines in Biologics

Licensed indications

In general, biological products are regulated (licensed for marketing) under the public health service act originally by the National Institutes of Health and its precursors, and later, starting in 1972, by the food and drug administration (FDA) and chemical drugs are regulated (approved for marketing) under the Federal Food Drug and Cosmetic Act – by the FDA.[4]

Biologic control act 1902

The regulation of biologics by the federal government began with the biologics control act of 1902, which was considered as the first enduring scheme of national regulation for any pharmaceutical product. There are two more acts which govern the rules and regulations of use of biologics, namely, pure food and drugs act and the public health service act.[5]

Guidelines and Recommended Guidance on the Use of Biologics for TNF-α and Rituximab

Eligibility

The severity of the disease or its resistance to standard systemic therapy determines the need for the use of biologics. Patient should be fully informed of risk and benefits of therapy and that treatment is off-label.

Contraindications

The contraindications for the use of biologics include hypersensitivity, active infections, severe heart failure (NYHA Class III/IV), pregnancy and lactation (Rituximab), and demyelination diseases.

Pre-treatment screening

A thorough history and complete physical examination must be done before treatment to identify possible contraindications to the treatment. A complete blood picture which includes liver function tests, tests and screening for HCV, HBV, and HIV is taken. Need for chest radiograph and vaccinations are assessed. However, liver vaccination is not administered.

Adverse events

The various adverse reactions that can occur include hypersensitivity reaction, exacerbation of cardiac failure, potential increase risk for malignancy, and other opportunistic infections. Hence, the patient is carefully monitored for early signs and symptoms of infection throughout treatment, any new onset or exacerbation of cardiac dysfunctions or any evidence of malignancy to prevent these adverse reactions.

Assessment of patient before treatment

Patient should be given the opportunities to select their preferred route of drug administration. They should always be informed about the drug therapy and should have signed the relevant consent forms of BSR biological registers and local trust policy.[6,7]

Patient monitoring

It is logical to take steps necessary to prevent infection in patient who is immunosuppressive by medication such as biological therapies.

Protocol before biologic therapy initiation

Before initiation of the therapy review the previous and current medication (including vaccination review) and obtain informed consent. Tests to be carried out before beginning the treatment includes: Cardiac function (cardiac failure is aggravated during TNF-α blockade), tuberculosis (TB) (skin testing; chest radiography), virus infections (HBV/HCV/HIV), and complete blood counts (CBC) to rule out potential risk of hepatic dysfunction, especially with Infliximab, liver function tests and take precautions for dealing with acute reactions to biologic agents.[8]

Assessment of patient during the course of treatment

Laboratory tests in monitoring patient on biological therapies are annual TB skin test; alternative include the QuantiFERON-TB gold blood test and chest X-ray if indicated; CD4+ T-lymphocyte count every 2 weeks for Alefacept; complete metabolic panel with liver function test for each Infliximab infusion and with signs of hepatic injury; +/− complete metabolic panel every 3–6 months on all biological therapies; +/− CBC every 3–6 months on all biological therapies and +/− hepatitis screen and HIV testing when risk factors present on all biological therapies.[9,10] In case of vaccination test for +/− influenza and pneumococcal vaccination, it may not be beneficial in patients taking Efalizumab.[7,8]

Regulatory Guidelines for the Development of Biologics

Validation of each step of development of biologics

The various steps involved in the process of development of biologics are as follows: Selection of target, target validation, screening preparation, hit generation and lead selection, lead optimization and characterization, and candidate selection.[11]

SOP guidelines

Standard operating procedure guidelines are a sequential procedure provided for manufacture and development of biologics which are essential for the quality. It should minimum include: Title page, header, department name, effective date, revision date, review date, page no, regulatory basis, reference documents, purpose, scope, responsibilities and accountabilities, procedure, footer, and stamp.[12]

Chemistry, manufacturing, and control (CMC) guidelines

CMC guidelines include the information regarding the manufacture, stability, and controls used in the manufacture of biologics. The assessment of CMC should include adequate characterization of the biologic, adequate characterization of impurities, adequate description of manufacturing, facilities available for manufacturing, quality control measures, and acceptable supporting information.[13]

Analytical tests to assess identity, purity, and concentrations

The success of development of biologics depends on the utilization of correct analytical methods for identification, purity analysis, and concentrations. Chromatographic methods, spectroscopic techniques, and peptide mapping are primarily used. Chromatographic methods are used for characterization of biophysical and chemical properties, formulation development, and in release testing and are common tools for physical and also chemical degradation. Spectroscopic techniques are used for qualitative and quantitative analysis of conformational structure of proteins, their behavior, and their stability in development and release. Peptide mapping is used for identification and purity testing which includes determination of primary amino acid chain, intact peptide fragments along with identification of specific degradation site. Other techniques include isoelectric focusing and capillary isoelectric focusing, SDC-PAGE, thermal analysis, particulate matter analysis, Karl-Fischer titration, and thermogravimetric analysis.[14]

Properties of Biologics

Biologics have properties such as self-association of the protein, dependence on molar absorption coefficient, solubility, pH stability,

thermal stability, and shear stability. Early propensities to form reversible and irreversible aggregates have significant effect on development of biologics. pH solubility is an important aspect which along with pH stability plays a key role in the development of biologics. Instability in storage conditions may lead to distortion and other conformational changes. Hence, biologics should have a thermal stability in addition to shear stability.[15]

Key Aspects of Guidelines for Biologics

TNF-α inhibitors

TNF-α is a key proinflammatory cytokine secreted by the T-cells and macrophages which is a pleiotropic actions that can be present both as a transmembrane protein and a soluble cytokine. It promotes increased leukocyte activity and has a significant role in the pathogenesis of immune-mediated disease through various pathways. Apart from oral diseases such as aphthous ulceration, oral CD, orofacial granulomatosis, pemphigus vulgaris, and Sjogren's syndrome, they have also been used to treat psoriasis and rheumatoid arthritis.

Administration mode for TNF-α inhibitors is similar to other biologic agents in the form of injected preparations with varying schedules. Infliximab must be given as periodic intravenous infusions, whereas Etanercept and Adalimumab are given as regular subcutaneous injections biweekly. Although it is associated with greater incidence of adverse effects, it is based on cost and potential risks.[16]

In patients with viral infections screening must be done before treatment with TNF-α because viral reactivation may occur. Anti-TNF therapy is given along with ART only in controlled cases of HIV infections where immune competence is not low and CD-4 count is under monitoring. Anti-TNF therapy may also cause reactivation of mycobacterial infections and screening is done before treatment. Risk of TB is increased in patients receiving Infliximab and Adalimumab and routine screening is essential.

Immunization and application of vaccines are of main concern since TNF-α inhibition causes risk of severe or fatal infections due to viral replication. Patients should receive influenza and pneumococcal immunizations before therapy for RA.[2]

Lymphocyte modulators

Lymphocyte modulators are immune regulating polypeptides which regulates CD-4 lymphocyte production and function. It is a single chain polypeptide with a cationic glycoprotein which has a molecular weight of 50,000 Daltons. The protein was shown to augment the immune responses of both the immature and mature T-cells and hence was known as lymphocyte T-cell immunomodulator. The bovine protein used is prepared in a lyophilized 1 microgram dose and its reconstruction in a sterile diluent produces a solution that is used to treat subcutaneous infections.

They can also be administered through injection preparations. Rituximab must be given as periodic intravenous infusions biweekly, whereas Alefacept is given as intramuscular injections weekly. Lymphocyte modulators can be differentiated as T-cell immunomodulators and B-cell immunomodulators. B-cell modulators have some effects on T-cells. Rituximab has specific effect on mature B-cells and acts by targeting CD-20 selectively depleting all circulating B-cells. T-cell modulators have an effect on specific CD antigens. Alefacept targets memory T-cells and NK-cells blocking CD2 interaction in antigen presentation and inducing T-cell apoptosis.

Screening for viral disease is done before treatment with Rituximab. Rituximab can be given in case of HIV and its associated infections, but Alefacept is strictly contraindicated since it reduces CD-4 count. TB Screening is not necessary in patients with RA receiving Rituximab. Rituximab should not be given in patients with serious or opportunistic infections; however, definitive guidance is unclear with regards to Rituximab. Rituximab causes severe infections and lowers IgG levels and hence should be used with caution.[2]

IL inhibitors

IL inhibitors are immunosuppressive agents which inhibits the action of ILs in regulating the immune system. There are various types of ILs. The inhibitors of IL-1 such as Anakinra, Rilonacept, or Canakinumab are used to treat diseases of joint, bone, and muscles as well as auto-inflammatory and inflammatory diseases.[17] IL-6 is a pleiotropic cytokine which when inhibited is effective in case of rheumatoid arthritis.

Tocilizumab is a monoclonal antibody which is specific and the first biologic agent targeting IL-6.[18] Although it is effective in the treatment of RA along with TNF-α inhibitors, its use is contraindicated when used with Etanercept due to its reduced efficacy.[19] Anakinra must not be used with TNF-α inhibitors such as Etanercept, Infliximab, and Adalimumab. Tocilizumab should not be given during acute infections and latent stage of TB.[20]

Informed Consent in Biologics

An informed consent according to the American Medical Association is the communication process between a patient and his or her physician that results in the patient's agreement to undergo a particular medical procedure or treatment. The concept of informed consent is rooted in medical ethics and codified as legal principle based on the assertion that a "Competent person has the right to determine what is done to him or her." Patients are entitled to informed decisions about their healthcare, but there is little to no guidance on the topic of informed consent for biologic infusions.

Hence, it is important to remember that the primary goal of the informed consent process is to convey significant safety information so the patient can decide whether or not to undergo the medical treatment. Sources of information include the product manufacturer, product or package labeling, medication guides, and continuing medical education.[6-10]

Conclusion

Thus, this article emphasizes the important aspects of guidelines on the use of biologics in treating various immune-mediated diseases which otherwise does not have any other treatment and the regulatory guidelines for its use. Although they have adverse effects in some patients, they can be used in recommended doses in patients whom other therapies have failed. Hence, it is important to know the regulatory guidelines and key aspects of guidelines for the use of biologics for safe and effective treatment of oral and other immune-mediated inflammatory conditions.

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