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A COMPREHENSIVE REVIEW OF INFLIXIMAB AS A TARGETED THERAPEUTIC CHOICE IN INFLAMMATORY DISORDERS

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ABSTRACT
Infliximab is a potent monoclonal antibody that has revolutionized the treatment of various inflammatory and autoimmune diseases. This captivating abstract takes you on a captivating journey through the world of infliximab, unraveling its mechanism of action, adverse effect, contraindication, outstanding efficacy. The drug infliximab was developed by Jan vilcek at New York university school of medicine and by the centocor company. Firstly, the drug infliximab approved by United States of America for the treatment of fistulizing disease and Crohn's disease. The drug infliximab first known as cA2, which is now marketed as Remicade. At the core of infliximab's triumph lies its remarkable ability to target tumor necrosis factor-alpha (TNF-α). Infliximab efficiently inhibits the inflammatory signaling system by preferentially binding to tumor necrosis factor-alpha (TNF-α), resulting in significant decreases in disease activity. Approximately 100% when administered intravenously due to its direct entry into the systemic circulation. This high bioavailability contributes to its consistent and predictable therapeutic effects. Many clinical studies demonstrated infliximab's excellent effectiveness. Infliximab is not manufactured chemically. It is a monoclonal antibody produced using recombinant DNA technology. While infliximab presents multiple benefits it is critical to be aware of any potential side effects. Among the recognized dangers of infliximab medication include infusion reactions, increased susceptibility to infections, and Malignancy and then it is contraindicated with heart failure, severe hypersensitivity reaction.

KEYWORDS: Remicade, monoclonal antibody, tumor necrosis factor-alpha, immunosuppressive agent.

DISCOVERY AND FURTHER HISTORY
Vilcek contributes to the creation of monoclonal antibody against the tumor necrosis factor–alpha Infliximab is the first ever used therapeutically in human.[1] In 1989 Vilcek and Junming Le at New York university school of medicine, and the Centocor Company were interested in developing the monoclonal antibody for ELISA test kits and the treatment of human diseases. As the Chief Scientific Officer at Centocor, they recruited James N. Woody, a former student of Maini and Feldmann, and this made it possible for anti-human anti- tumor necrosis factor monoclonal antibodies to be made available for a modest clinical study on 10 Rheumatoid arthritis patients. The trial that began in May 1992 produced unexpected outcomes. Patients experienced significant clinical improvement as well as a reduction in inflammation. Marc Feldmann publicly announced the great success of Centocor's anti- tumor necrosis factor monoclonal antibodies and then it is known as "infliximab," in a small group meeting hosted by David Naor in Israel, in September 1992. The outcomes of the meeting were then published.

Vilcek and Le contributed to the creation of the biologic medication first known as cA2, which is now marketed as infliximab or Remicade. It used to treat Rheumatoid arthritis, plaque psoriasis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, and other inflammatory illnesses. It is a strong anti-inflammatory drug. The first TNF blocking medication used with effectiveness in patients was infliximab.[2]

APPROVAL HISTORY OF INFLIXIMAB
- In August 24, 1998, Infliximab was approved by United States of America for the treatment of

fistulizing disease and moderate-to-severe Crohn's disease in patients.[3]

- In August 1999, Infliximab was approved by the European Union for the treatment of severe, active Crohn's disease and fistulizing disease.[4]
- In December 2001, Infliximab was the first TNF-alpha inhibitor to be approved in Japan for the treatment of moderate-to-severe Crohn's disease.
- In February 2002, United States of America approved the drug Infliximab for the treatment of moderate to severe Rheumatoid arthritis.
- In June 2002, the FDA first approved Infliximab as a TNF-alpha inhibitor for the treatment in severe Crohn's disease.
- Infliximab was the first TNF-alpha inhibitor permitted in the European Union in May 2003 for the treatment of ankylosing spondylitis in patients with severe axial symptoms.
- In October 2004, Infliximab used for the treatment of active and progressing psoriatic arthritis.
- December 17, 2004, Food and Drug Administration approved the drug Infliximab for the treatment ankylosing spondylitis.
- In the European Union (EU), Infliximab was the first biologic drug to be authorized in March 2006 for the treatment of individuals with moderately to highly active ulcerative colitis.
- September 26, 2006, Food and Drug Administration approved the drug Infliximab for plaque psoriasis.
- The initially Food and Drug Administration authorized Infliximab in September 23, 2011, as a TNF-alpha inhibitor for treatment of pediatric ulcerative colitis.[3]

PHYSICAL PROPERTIES

The physical properties of drug shown below[5,6]

Appearance	Infliximab is commonly available as a lyophilized powder for reconstitution.
Color	White to off-white (powder), After Reconstitution the resulting solution is usually clear to slightly opalescent and may be colorless or pale yellow.
Solubility	>10 mg/mL in sterile water.
Melting point	71°C
pH	7.2
Storage Conditions	Infliximab should be stored in a refrigerator at a temperature between 2°C to 8°C (36°F to 46°F)
Particle Size	0.2 to 0.5 micrometers
Osmolality	Infliximab solutions typically range from around 280 to 380 mOsm/kg.

PHARMACOKINETIC PROPERTY

BCS classification	Infliximab, the monoclonal antibody used to treat various autoimmune conditions, including rheumatoid arthritis and inflammatory bowel disease, is classified under BCS Class III. BCS Class III drugs have high solubility but low permeability
Bioavailability	100%[5]
Molecular-weight	141.9 kDa
Onset of Action	2 weeks
Duration of Action	12 weeks
Half-life	Half-life ranged from 7 to 12 days
mean residence time	12-17 days
Volume of distribution	3-6 L
Clearance	11-15 mL/h[7]
Cmax	At single doses of 3, 5, or 10 mg/kg, the median Cmax values were 77, 118 and 277 micrograms/ml[8]
Absorption	Infliximab is injected intravascularly so it has no absorption characteristics.
Distribution	Infliximab is largely dispersed into the blood; its apparent

	median steady state volume of distribution of 57.2 to 80 mL/kg approximated to 4.0 to 5.60 liters in a 70 kg person corresponds to the total blood volume.[9]
Elimination	Elimination of infliximab is most probably accomplished through degradation by unspecific proteases.[7]
Metabolism	Infliximab is processed in the body in the same way as other proteins are. It is most likely hydrolyzed into amino acids and recycled or catabolized.
Excretion	After intravenous administration, infliximab as a complete molecule was not identified in the urine.[9]

MECHANISM OF ACTION

The primary mechanism of action of infliximab is the binding and neutralization of tumor necrosis factor-alpha (TNF-α), a cytokine involved in immune and inflammatory responses. By binding to both soluble and membrane-bound tumor necrosis factor-alpha (TNF-α), infliximab prevents tumor necrosis factor-alpha (TNF-α) from binding to its receptors, p55 and p75. This interference with tumor necrosis factor-alpha (TNF-α) signaling helps to reduce the hyperactive immune response seen in autoimmune disorders such as rheumatoid arthritis, irritable bowel disease (IBD) and psoriasis thereby alleviating localized symptoms like inflammation, swelling, and joint pain.

In addition to its primary mechanism, infliximab has a secondary mechanism of action called Fc-mediated apoptosis. This mechanism involves the binding of the Fc portion of infliximab to natural killer cells, which can initiate a signaling cascade. This cascade leads to the apoptosis (cell death) of immune cells, particularly monocytes and macrophages expressing transmembrane tumor necrosis factor-alpha (TNF-α). Another aspect of Fc-mediated apoptosis involves the binding of infliximab's Fc region to C1q proteins, which triggers the development of a membrane attack complex (MAC). The membrane attack complex then causes the destruction of cells expressing transmembrane tumor necrosis factor-alpha (tmTNF-α).

Overall, infliximab's primary mechanism involves neutralizing tumor necrosis factor-alpha (TNF-α) to modulate the immune response, while the secondary mechanism, Fc-mediated apoptosis, contributes to the therapeutic effect in irritable bowel syndrome patients by promoting the apoptosis of inflammatory cells. By reducing the number of cells involved in overactive immune responses, infliximab helps alleviate the symptoms of irritable bowel disease.[10]

METHODS OF INFLIXIMAB PRODUCTION

Infliximab is not produced chemically. It is a monoclonal antibody made by the use of recombinant DNA technology, which is based on biological processes rather than synthetic chemical processes.[11]

The production of infliximab involves the insertion of human antibody genes into a mouse host organism. The first step in making infliximab is to isolate the DNA from a human cell line, typically a lymphocyte. The DNA is then placed into a plasmid, a tiny, circular DNA molecule that can replicate on its own and is often employed in molecular biology. The plasmid is then transferred by a procedure known as transformation into a mouse cell line, such as a Chinese hamster ovary (CHO) cell line. The CHO cells are cultured in a controlled environment, such as a bioreactor, where they are driven to produce the human antibody genes when the plasmid has been successfully inserted. After that, the generated antibodies are removed from the cell culture and purified through a process that includes filtration, centrifugation, and chromatography. The usage of a protein a affinity column chromatography is one of the important phases in the purification procedure. This column has a protein a molecule coated on it that binds to the Fc region of the infliximab molecule and allows the antibody to be separated from other impurities in the cell culture.[12,13]

Once purified, infliximab is concentrated to achieve the desired concentration for the final product. Usually, ultrafiltration or diafiltration methods are used to concentrate the antibody solution and remove extra water. Numerous additives have been added to the concentrated infliximab solution during formulation to guarantee stability and prolong shelf life. These additives could consist of stabilizers to stop aggregation or degradation, buffers to keep the pH stable, sugars or polyols to act as cryoprotectants for freeze-dried formulations, or preservatives to inhibit microbiological development in multi-dose vials. The infliximab solution goes through sterile filtering after formulation to get rid of any potential microbiological contamination. This procedure is critical for ensuring the finished product's stability. The finished mixture is then aseptically poured into vials or pre-filled syringes. The containers are labeled with pertinent details, including dose strength, lot quantity, and date of expiry and are sealed.[14,15] In the traditional sense, monoclonal antibodies are not considered conventional dosage forms. These are a type of biopharmaceutical medication that is created by cloning cell lines to create large quantities of specific antibodies.

The chemical structure of infliximab was discovered through a combination of methods, including protein sequencing and analysis, as well as mass spectrometry.

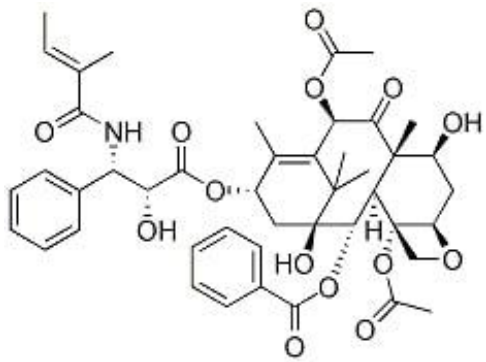

Fig. no. 1: Chemical structure of infliximab.

MEDICINAL USES

Crohn's disease

Crohn disease is a kind of inflammatory bowel disease (IBD). Crohn's disease typically affects the gastrointestinal tract, which causes fever, severe diarrhea, fatigue, and weight loss. Infliximab is used to treat both adults and children with mild to severe Crohn's disease.[16]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a disorder described by an immune-mediated inflammatory synovitis that damages joint cartilage and bone. Tumor necrosis factor-alpha, interleukin-1, and interleukin-6 are released by the inflammatory cells. The medication called Infliximab is used to treat rheumatoid arthritis. Because Infliximab binds to both soluble and trans-membrane tumor necrosis factor-alpha with high affinity, it can reduce synovial inflammation, bone resorption, and cartilage degradation.[17]

Ulcerative colitis

Ulcerative colitis is a chronic inflammatory bowel disease. In ulcerative colitis, tumor necrosis factor -alpha causes chronic inflammation and tissue destruction in the colon and rectum. Tumor necrosis factor-alpha inhibitors, such as infliximab, are used to block this effect, lowering inflammation and improving patient condition.[18]

Psoriatic arthritis

Infliximab is prescribed for adult patients with psoriatic arthritis to lessen the signs and symptoms of active arthritis, such as joint discomfort and extra-articular manifestations such dactylitis, enthesitis, and nail disease, as well as psoriatic skin involvement, and to enhance physical function.[19]

Ankylosing spondylitis

Ankylosing spondylitis (AS) is a long-term inflammatory condition that mostly affects the spine and results in swelling, discomfort, and stiffness. It is a member of the class of diseases known as spondyloarthropathies. In individuals with Ankylosing spondylitis, infliximab causes a rapid decline in disease activity. Tumor necrosis factor-alpha inhibitors influence the underlying inflammation of both articular and extra-articular symptoms of Ankylosing spondylitis.[20]

Plaque Psoriasis

Infliximab is used in the treatment of adult patients with chronic severe (extensive and/or disabling) plaque psoriasis. (Leman J et al.)Infliximab is an excellent therapy for persistent plaque psoriasis, with 90% of patients becoming clear or having low disease activity after 5 mg/kg administered at weeks 0, 2, and 6.[21]

ADVERSE EFFECTS

Although infliximab is typically a safe and well-tolerated drug, the possibility of adverse effects rises with dosage or patient age (more than 60 years). Some important adverse effects are,

- Heart failure
- Hypertension
- Constipation
- Diarrhea
- Paradoxical reaction
- Malignancy
- Hepatotoxicity
- Reactivation of hepatitis B
- Psoriasis
- Tuberculosis reactivation
- Demyelination disease
- Vitiligo
- Anemia, leukopenia, neutropenia, thrombocytopenia
- Lupus-like syndrome
- Infusion-related reactions like fever, pruritus, anaphylaxis.[22,23]

TREATMENT OF OVERDOSE

Healthcare professionals often give infliximab in a hospital environment. Toxicology is quite unusual. Therefore, infliximab toxicity is not specifically treated. In such a case, supportive care is the recommended course of action. Infliximab overdose has no particular antidote. Symptomatic therapy may be given, depending on the symptoms that are currently present.[24,25]

CONTRAINDICATIONS

- Infliximab is not recommended for people with mild to severe heart failure.
- Infliximab is not recommended for patients with tuberculosis or other serious illnesses.
- It is not advised for individuals who have experienced an intense hypersensitivity reaction to take infliximab
- Infliximab is not recommended for patients who have a blood/bone marrow disorder, a nervous system illness, cancer, or a lung disorder.[25]

INTERACTION

The medicines listed below may interact with Infliximab.[26,27]

Drug Category	Examples	What can occur
Immunosuppressant Drugs	• Methotrexate (Otrexup, Rasuvo) • Azathioprine (Azasan, Imuran) • Sirolimus (Fyarro, Rapamune) • Cyclosporine (Gengraf, Neoral, Sandimmune) • Tacrolimus (Astagraf XL, Envarsus XR, Prograf)	Can increase the possibility of Infliximab adverse effects.
Corticosteroids	• Methylprednisolone (Depo-Medrol, Medrol, Solu-Medrol) • Prednisone (Rayos) • Dexamethasone (Hemady)	Can increase the possibility of Infliximab adverse effects.
Other Biologic Drugs	• Abatacept (Orencia) • Adalimumab (Humira) • Anakinra (Kineret) • Etanercept (Enbrel) • Tocilizumab (Actemra)	Can increase the possibility of Infliximab adverse effects.
Live vaccines	• Yellow fever • Varicella (chickenpox) • Cholera • Nasal influenza mist (FluMist) • Rotavirus • Smallpox • Oral typhoid	infliximab weakens immune system

NOVEL MARKETED FORMULATIONS

Drug Types	brand name	company name	dose	prize
Powder	Remicade	Janssen biologics B.V	100 Mg	₹ 13,000/ Vial

PATENT

Janssen Biotech, Inc., a Johnson & Johnson company, owns the patent for infliximab. The infliximab patent offers legal protection for the drug's creation by prohibiting anyone from producing, using, or dispensing it without the patent holder's consent.

A specific patent for infliximab is US Patent No. 5,698,227, "Chimeric Antibodies with Receptor Binding Ligands in Place of Their Constant Region." On December 16, 1997, it was approved after being filed on December 22, 1994. Jan Vilcek and Bruce D. Sollinger are the named inventors of the patent. This patent covers the creation of chimeric antibodies, which replace their constant region with receptor-binding ligands.[28]

CONCLUSION

Infliximab is a monoclonal antibody that targets tumor necrosis factor alpha and efficiently lowers inflammation in individuals suffering from rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis. Infliximab reducing disease activity and improving patient condition. Looking to the future, the allure of infliximab continues to grow. Ongoing research aims to refine dosing strategies, explore combination therapies, and expand its utility to novel indications. Infliximab is a costly drug, and its availability may be limited in some healthcare systems. However, the emergence of biosimilar versions has given more economical options, boosting access to this vital medicine.

Despite its numerous advantages, it is vital to be aware of the hazards connected with Infliximab, which include infusion reactions, infections, and an increased risk of some malignancies. To control these hazards and maintain patient safety, proper monitoring and screening are required.

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