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A review on recombinant drugs

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Abstract
Over the last century, enormous progress has been made in preventing, alleviating and curing diseases. These developments can be linked to progress in the fields of molecular biology and genetic engineering. Insulin is one of the best examples of how the combined knowledge and application of these scientific disciplines has led to successful disease therapy. This review article explains the importance of recombinant drugs, their treatment methodology, and their adverse effects. Various newer recombinant molecules are available in the market for treatment and cure of various diseases and disorder. This paper focus on Intron A, Muromonab, Roferon, Interferon, Monoclonate. It also enclosed dose, clinical pharmacology, side effects, storage, uses of the drugs.

Keywords: Recombinant Drugs, molecules, Insulin

Introduction
To date, biotechnology has produced more than 200 new therapies and vaccines, including products to treat cancer, diabetes, HIV/AIDS, and autoimmune disorders. There are more than 400 biotech drug products and vaccines currently in clinical trials, targeting more than 200 diseases, including various cancers, Alzheimer' s disease, heart disease, diabetes, multiple sclerosis, AIDS, and arthritis. This trend is supported by new or adapted approved routes from the regulatory bodies such as the EMA (European Medicines Agency) and the FDA (Food and Drug Administration) An average approval of 10 – 15 products a year indicates that pharmaceutical biotechnology is a highly active sector. Amongst these, the number of genuinely new biopharmaceuticals is around 40%, indicating the high innovative character of research; some of these products are likely to be future blockbusters. Examples are monoclonal antibody - based products such as Rituximab (Rituxan ®/MabThera ®) for the treatment of cancer with $18 billion in sales in 2009, insulin and insulin analogues ($13.3 billion/2009), and finally erythropoietin - based products ($9.5 billion/2009).

Intron A
Intron A (interferon alfa-2b, recombinant for injection) is one commercial form of interferon approved by the US Food and Drug Administration for the treatment of Hepatitis B and C.

Route of Administration: INTRON® A (interferon alfa-2b,) (Interferon alfa-2b) for intramuscular, subcutaneous, intralesional, or intravenous Injection is a purified sterile recombinant interferon product.
INTRON® A is water-soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon alfa-2b gene from human leukocytes. The fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline hydrochloride at a concentration of 5 to 10 mg/L; the presence of this antibiotic is not detectable in the final product. The specific activity of Interferon alfa-2b, recombinant is approximately 2.6 x 10^8IU/mg protein as measured by the HPLC assay.

Clinical Pharmacology
General: The interferons are a family of naturally occurring small proteins and glycoproteins with molecular weights of approximately 15,000 to 27,600 daltons produced and secreted by cells in response to viral infections and to synthetic or biological inducers.
Preclinical Pharmacology: Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events. In vitro studies demonstrated that these include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells. In a study using human hepatoblastoma cell line HB 611, the in vitro antiviral activity of alpha interferon was demonstrated by its inhibition of hepatitis B virus (HBV) replication.

Side Effect
- Fast, slow, or uneven heart rate, feeling like you might pass out;
- Severe depression, aggressive behavior, or thoughts of hurting yourself or others;
- Fever, chills, body aches, flu symptoms, pale skin, easy bruising or bleeding, unusual weakness;
- Vision or hearing problems;
- Urinating less than usual or not at all;
- Severe stomach pain, jaundice (yellowing of the skin or eyes);
- Cough with yellow or green mucus, feeling short of breath;

- Chest pain, pain spreading to the arm or shoulder, nausea, sweating, general ill feeling;
- Sudden numbness or weakness, headache, confusion, or problems with speech or balance; or
- A severe blistering, peeling, and red skin rash.

Less serious side effects may include
- Dizziness, spinning sensation;
- Muscle pain, tired feeling;
- Nausea, vomiting, diarrhea, loss of appetite;
- Dry mouth, dry cough, sore throat, hair loss;
- Mild itching or skin rash; or
- Burning, bleeding, pain, itching, or skin changes where the medicine was injected.

Uses
This medication is used to treat various cancers (e.g., leukemia, melanoma, AIDS-related Kaposi's sarcoma). It is also used to treat virus infections (e.g., chronic hepatitis B, chronic hepatitis C, condylomata acuminata). This medication is the same as a protein that your body naturally produces (interferon). In the body, it is thought to work by affecting cell function/growth and the body's natural defenses (immune system) in many ways. Adding more interferon may help your body fight off cancer or virus infections.

Precautions
Alpha interferons, including INTRON® A (interferon alfa-2b, recombinant for injection), cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.

Doses
The FDA-approved dose of standard interferon alfa for treatment of hepatitis. FDA-approved treatment for hepatitis B is five million units daily for 16 weeks. The dose may be modified for significant side effects.

OKT3 / muromonab-CD3 /Orthoclone OKT3
- **Pharmacologic class:** Murine monoclonal antibody
- **Therapeutic class:** Immunosuppressant

Muromonab-CD3 (trade name Orthoclone OKT3, marketed by Janssen-Cilag) is an immunosuppressant drug given to reduce acute rejection in patients with organ transplants. It is a monoclonal antibody targeted at the CD3 receptor, a membrane protein on the surface of T cells. It was the first monoclonal antibody to be approved for clinical use in humans.

General Pharmacology
Binds to and blocks function of T lymphocytes responsible for antigen recognition, thereby reversing graft rejection T cells recognise antigens primarily via the T cell receptor. This receptor needs various co-receptors to function, one of which is CD3. The T cell receptor-CD3 complex transduces the signal for the T cell to proliferate and attack the antigen.
Muromonab-CD3 is a murine (mouse) monoclonal IgG2a antibody which was created using hybridoma technology. It binds to the T cell receptor-CD3-complex (specifically the CD3 epsilon chain) on the surface of circulating T cells, initially leading to an activation, but subsequently inducing blockage and apoptosis of the T cells. This protects the transplant against the T cells [2, 4]. After application of muromonab-CD3, normal T cell function is said to be restored within a week. When administered for transplant induction, the drug is administered daily thereafter for up to 7 days.

Contraindications
- Hypersensitivity to drug or other murine products
- Uncompensated heart failure
- Uncontrolled hypertension
- Predisposition to or history of seizures
- Antimouse antibody titer of 1:1000 or higher
- Pregnancy or breastfeeding

Adverse Reactions
- **CNS:** fatigue, headache, weakness, tremors, hallucinations, aseptic meningitis, cerebral edema, seizures, encephalopathy
- **CV:** chest pain, hypertension, hypotension, heart failure, tachycardia, cardiac arrest, shock
- **EENT:** vision loss, blurred vision, conjunctivitis, photophobia, tinnitus, otitis media
- **GI:** nausea, vomiting, diarrhea
- **GU:** oliguria, anuria
- **Respiratory:** dyspnea, wheezing, severe pulmonary edema, adult respiratory distress syndrome (ARDS)
- **Skin:** flushing
- **Other:** fever, chills, flulike symptoms, infection, anaphylaxis, cytokine release syndrome

Less common
- Chest pain
- rapid or irregular heartbeat
- shortness of breath or wheezing
- swelling of face or throat

More common
- Diarrhea
- dizziness or faintness
- fever and chills
- general feeling of discomfort or illness
- headache
- muscle or joint pain
- nausea and vomiting

FDA Warning
- Give under supervision of physician experienced in immunosuppressive therapy and management of solid-organ transplant patients, in facility equipped for cardiopulmonary resuscitation where patient can be monitored closely based on health status.
- Drug may cause anaphylactic and anaphylactoid reactions and occasionally life-threatening or lethal systemic, cardiovascular, and CNS reactions. Monitor patient's fluid status closely before and during therapy. Methylprednisolone pretreatment is recommended to minimize symptoms of cytokine release syndrome.

ROA*:* 1 mg/1 ml in 5-ml ampules
Indications and dosages
Acute allograft rejection in kidney transplant patients; steroid-resistant acute allograft rejection in heart and liver transplant patients

Uses for Orthoclone OKT 3
Muromonab-CD3 is a monoclonal antibody. It is used to reduce the body's natural immunity in patients who receive organ (for example, kidney) transplants.
When a patient receives an organ transplant, the body's white blood cells will try to get rid of (reject) the transplanted organ. Muromonab-CD3 works by preventing the white blood cells from doing this.
The effect of muromonab-CD3 on the white blood cells may also reduce the body's ability to fight infections. Before you begin treatment, you and your doctor should talk about the good this medicine will do as well as the risks of using it.

Monoclonate
Antihemophilic Factor (Human) Factor VIII: C Pasteurized Monoclonal Antibody Purified.
Monoclate-P® is indicated for the treatment of classical hemophilia (hemophilia A). Over a decade of clinical experience and efficacy supported by over 1 billion international units (IU) of use. The manufacturing process combines nature's own design - the human factor VIII molecule - with innovations in laboratory engineering: monoclonal antibody purification and pasteurization designed to remove and inactivate lipid-enveloped and certain non-lipid-enveloped viruses a demonstrated level of consistent potency.
A murine monoclonal antibody to VWF: Ag is used as an affinity ligand to first isolate the Factor VIII Complex. Factor VIII: C is then dissociated from VWF: Ag, recovered, formulated and provided as a sterile lyophilized powder. The concentrate as formulated contains Albumin (Human) as a stabilizer, resulting in a concentrate with a specific activity between 4 and 10 units/mg of total protein. Monoclate-P® has been prepared from pooled human plasma and is intended for use in therapy of classical hemophilia (Hemophilia A). All Source Plasma used in the manufacture of this product was tested by FDA-licensed Nucleic Acid Tests (NAT) for HCV and HIV-1 and found to be nonreactive (negative).

Clinical Pharmacology
Factor VIII: C is the coagulant portion of the Factor VIII complex circulating in plasma. It is noncovalently associated with the von Willebrand protein responsible for von Willebrand factor activity. These two proteins have distinct biochemical and immunological properties and are under separate genetic control. Factor VIII:C acts as a cofactor for Factor IX to activate Factor X in the intrinsic pathway of blood coagulation.8 Hemophilia A, a hereditary disorder of blood coagulation due to decreased levels of Factor VIII:C, results in profuse bleeding into joints, muscles or internal organs as a result of a trauma. Monoclate-P® provides an increase in plasma levels of AHF, thereby enabling temporary correction of Hemophilia A bleeding.

Adverse Reactions
Products of this type are known to cause allergic reactions, mild chills, nausea or stinging at the infusion site.

Dosage and Administration
Monoclate-P® is for intravenous administration only. As a general rule 1 unit of AHF activity per kg will increase the circulating AHF level by 2%. The following general dosages are suggested in different conditions:
1. **Mild Hemorrhages:** Minor hemorrhagic episodes will generally subside with a single infusion if a level of 30% or more is attained.
2. **Moderate Hemorrhage and Minor Surgery:** For more serious hemorrhages and minor surgical procedures, the patient's Factor VIII level should be raised to 30-50% of normal, which usually requires an initial dose of 15-25 I.U. per kg. If further therapy is required a maintenance dose is 10-15 I.U. per kg every 8-12 hours.
3. **Severe Hemorrhage:** In hemorrhages near vital organs (neck, throat, subperitoneal) it may be desirable to raise the Factor VIII level to 80-100% of normal which can be achieved with an initial dose of 40-50 I.U. per kg and a maintenance dose of 20-25 I.U. per kg every 8-12 hours.
4. **Major Surgery:** For surgical procedures a dose of AHF sufficient to achieve a level 80-100% of normal should be given an hour prior to surgery. A second dose, half the size of the priming dose, should be given five hours after the first dose. Factor VIII levels should be maintained at a daily minimum of at least 30% for a period of 10-14 days postoperatively.

Indications and Usage
Monoclate-P® is indicated for treatment of classical hemophilia (Hemophilia A). Affected individuals frequently require therapy following minor accidents. Surgery, when required in such individuals, must be preceded by temporary corrections of the clotting abnormality. Surgical prophylaxis in severe AHF deficiency can be accomplished with an appropriately-dosed pre-surgical IV bolus of Monoclate-P® followed by intermittent maintenance doses.

Storage
When stored at refrigerator temperature, 2-8 °C (36-46 °F), Monoclate-P® is stable for the period indicated by the expiration date on its label. Within this period, Monoclate-P® may be stored at room temperature not to exceed 25 °C (77 °F), for up to 6 months.
Avoid freezing which may damage container for the diluent.

Important Safety Information
- Monoclate-P® is contraindicated in patients with known hypersensitivity to mouse protein.
- Products of this type are known to cause allergic reactions, mild chills, nausea or stinging at the infusion site. In some cases, inhibitors of FVIII may occur.

Roferon-A
- **Pharmacologic class:** Biological response modifier
- **Therapeutic class:** Antineoplastic, antiviral

FDA Boxed Warning
Drug may cause or worsen fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor patient closely with periodic clinical and laboratory evaluations. Discontinue drug in patients with

persistently severe or worsening signs or symptoms of these conditions. In many cases, these disorders resolve after withdrawal.

Description

Roferon-A (Interferon alfa-2a, recombinant) is a sterile protein product for use by injection. Roferon-A is manufactured by recombinant DNA technology that employs a genetically engineered Escherichia coli bacterium containing DNA that codes for the human protein. Interferon alfa-2a, recombinant is a highly purified protein containing 165 amino acids, and it has an approximate molecular weight of 19,000 daltons. Fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline hydrochloride, 5 mg/L. However, the presence of the antibiotic is not detectable in the final product. Roferon-A is supplied in prefilled syringes. Each glass syringe barrel contains 0.5 mL of product. In addition, there is a needle, which is ½ inch in length.

Availability/Route of Administration Alfa-2a

Injection (single-use vials): 3 million, 6 million, 9 million, and 36 million international units

Injection (multidose vials): 9 million and 18 million international units

Sterile powder for injection: 18 million international units with diluent

Alfa-2b

Injection: 3 million international units/0.5-ml vial, 5 million international units/0.5-ml vial, 10 million international units/1-ml vial; 18 million international units/3.2-ml vial, 25 million international units/3.2 ml vial

Powder for injection (vial with diluent): 3 million, 5 million, 10 million, 18 million, 25 million, and 50 million international units

Administration

- Give alfa-2a by subcutaneous or I.M. route. Reconstitute with 3 ml of diluent provided; swirl gently to dissolve.
- Administer alfa-2b by subcutaneous, I.M., or I.V. route. For I.V. use, reconstitute with diluent provided (bacteriostatic water for injection), according to chart provided. Mix gently, draw drug up into sterile syringe, and inject into 100 ml of normal saline solution. Infuse slowly over 20 minutes. Give antiemetics, as needed and prescribed, for nausea and vomiting.

Contraindications

- Hypersensitivity to drug or its components
- Autoimmune disorders
- Female partners of males receiving drug

Precautions; Use Cautiously In

- Cardiac or pulmonary disease; bone marrow, autoimmune, seizure, or psychiatric disorders
- Diabetic patients prone to ketoacidosis
- Pregnant or breastfeeding patients
- Children.

Adverse Reactions

- **CNS:** dizziness, confusion, paresthesia, rigors, lethargy, depression, difficulty thinking or concentrating, insomnia, anxiety, fatigue, asthenia, amnesia, malaise, nervousness, drowsiness, suicidal ideation
- **CV:** chest pain, hypertension, palpitations, arrhythmias
- **EENT:** visual disturbances, stye, hearing disorders, nasal congestion, sinusitis, rhinitis, pharyngitis
- **GI:** nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, flatulence, eructation, stomatitis, dry mouth, intestinal obstruction
- **GU:** gynecomastia, impaired fertility in women, transient erectile dysfunction
- **Hematologic:** anemia, leukopenia, thrombocytopenia, neutropenia
- **Metabolic:** hyperglycemia, hypocalcemia
- **Musculoskeletal:** joint pain, back pain, myalgia
- **Respiratory:** cough, dyspnea
- **Skin:** flushing, rash, dry skin, pruritus, alopecia, dermatitis, diaphoresis
- **Other:** gingivitis, flulike symptoms, candidiasis, edema, weight loss

Clinical Pharmacology

The mechanism by which Interferon alfa-2a, recombinant, or any other interferon, exerts antitumor or antiviral activity is not clearly understood. However, it is believed that direct antiproliferative action against tumor cells, inhibition of virus replication and modulation of the host immune response play important roles in antitumor and antiviral activity.

Indications and Usage

Roferon-A is indicated for the treatment of chronic hepatitis C and hairy cell leukemia in patients 18 years of age or older. In addition, it is indicated for chronic phase, Philadelphia chromosome (Ph) positive chronic myelogenous leukemia (CML) patients who are minimally pretreated (within 1 year of diagnosis).

For Patients with Chronic Hepatitis C

Roferon-A is indicated for use in patients with chronic hepatitis C diagnosed by HCV antibody and/or a history of exposure to hepatitis C who have compensated liver disease and are 18 years of age or older. A liver biopsy and a serum test for the presence of antibody to HCV should be performed to establish the diagnosis of chronic hepatitis C. Other causes of hepatitis, including hepatitis B, should be excluded prior to therapy with Roferon-A.

Contraindications

Roferon-A is contraindicated in patients with:

- Hypersensitivity to Roferon-A or any of its components
- Autoimmune hepatitis
- Hepatic decompensation (Child-Pugh class B and C) before or during treatment
- Roferon-A is contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol is associated with an increased incidence of neurologic and other complications in neonates and infants, which are sometimes fatal.

Warning

This medication can infrequently cause or worsen serious (rarely fatal) medical conditions, including mental/mood

conditions (e.g., depression), immune system problems (autoimmune conditions such as lupus or rheumatoid arthritis), circulation problems, or infections. If your medical history includes any of these conditions, tell your doctor promptly. Also, tell your doctor immediately if any serious symptoms or side effects occur (see Side Effects section).

Uses

This medication is used to treat various cancers (e.g., leukemia, melanoma, AIDS-related Kaposi's sarcoma). It is also used to treat virus infections (e.g., chronic hepatitis B, chronic hepatitis C, condylomata acuminata). This medication is the same as a protein that your body naturally produces (interferon). In the body, it is thought to work by affecting cell function/growth and the body's natural defenses (immune system) in many ways. Adding more interferon may help your body fight off cancer or virus infections.

- Chronic hepatitis C
- Chronic hepatitis B
- Hairy cell leukemia
- AIDS-related Kaposi's sarcoma
- Chronic myelogenous leukemia (Philadelphia chromosome-positive)
- Malignant melanoma (as adjunct to surgery)
- Condyloma acuminatum (genital or venereal warts)
- Aggressive follicular non-Hodgkin's lymphoma

Storage

The prefilled syringe should be stored in the refrigerator at 36° to 46 °F (2° to 8 °C). Do not freeze or shake. Protect Roferon-A (interferon alfa-2a, recombinant) from light during storage.

Conclusion

Recombinant technology has indeed made tremendous breakthrough in the discovery of various recombinant products. Besides the products approved by FDA for human use, several products are undergoing clinical trials. Products developed in the field of haematology, endocrinology and oncology will be most valuable for further development of recombinant products in the coming years.

References

1. Reichert JM, Paquett C. Therapeutic recombinant proteins: Trends in US approvals 1982–2002. Curr Opin Mol Ther. 2003: 5:139–147.
2. Hockney R. Recent developments in heterologous protein production in E. coli Trends Biotechnol. 1994; 12:456–463.
3. Gerngross TU. Advances in the production of human therapeutic proteins in yeasts and filamentous fungi. Nature Biotechnol. 2004; 22:1409–1414.
4. Wurm FM. Production of recombinant protein therapeutics in cultivated mammalian cells. Nature Biotechnol. 2004; 22:1358–1393.
5. Lubon H. Transgenic animal bioreactors in biotechnology and production of blood proteins. Biotechnol Annu Rev. 1998, 4:1– 54.
6. Hiripi L, Makovics F, Halter R, Baranyi M, Paul D, Carnwath JW *et al.* Expression of active human blood clotting factor VIII in mammary gland of transgenic rabbits. DNA Cell Biol. 2003; 22:41–45.
7. Ma JKC, Drake PMW, Christou P. The production of recombinant pharmaceutical proteins in plants. Nature Rev Genet. 2003; 4:794–805.
8. Fischer R, Stoger E, Schillberg S, Christou P, Twyman RM. Plant based production of biopharmaceuticals. Curr. Opin. Plant Biol. 2004; **7**:152–158.