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REVIEW ARTICLE ON ANAKINRA INJECTION

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ABSTRACT :

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder primarily affecting the synovial joints. Characterized by persistent inflammation, synovial hyperplasia, and progressive joint destruction, RA leads to significant pain, stiffness, swelling, and reduced mobility. The exact etiology remains unclear, but a combination of genetic predisposition and environmental factors, such as infections and smoking, contribute to its pathogenesis. The disease involves an aberrant immune response wherein autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), play a crucial role. Diagnosis is based on clinical symptoms, serological markers, and imaging studies. Management of RA includes pharmacological therapies—nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biologics—along with physical therapy and lifestyle modifications. Early diagnosis and aggressive treatment are essential to prevent irreversible joint damage and maintain quality of life. Current research focuses on targeted therapies and personalized medicine to improve long-term outcomes

KEYWORD: Rheumatoid Arthritis, Autoimmune Disease, Disease-Modifying Antirheumatic Drugs (DMARDs), Anakinra, Parenteral Formulations, Interleukin-1 Inhibitors

RHEUMATOID ARTHRITIS

A chronic progressive inflammatory musculoskeletal disease affecting multiple joints, connective tissue, muscle, tendon, and fibrous tissue is termed rheumatoid arthritis.

Rheumatoid arthritis is an autoimmune condition, which means it's caused by the immune system attacking healthy body tissue.

Rheumatoid arthritis affects joint linings, causing painful swelling. Over long periods of time, the inflammation associated with rheumatoid arthritis can cause bone erosion and joint deformity.

While there is no cure for rheumatoid arthritis, physiotherapy, and medication can help slow the disease's progression. Most cases can be managed with a class of medications called anti-rheumatic drugs (DMARDs) and biologics.

Women are 2 to 3 times more likely to get RA than men. And although symptoms most commonly develop between the ages of 30 and 60, younger people can also be affected.

JUVENILE RHEUMATOID ARTHRITIS

This term denotes the presence of Rheumatoid Arthritis in paediatric patients (less than 17 years of age)

ETIOLOGY

RA is an autoimmune disorder occurring when the immune system attacks the synovium (lining of the membranes surrounding the joints). As a results, the synovium becomes inflamed and thickness which ultimately destroys the cartilage and bone within the joint. The tendons and ligaments holding the joint become weak and stretched, thus the joints eventually lose their shape and size.

PATHOGENESIS:

- T and B cells are flavour the production of autoantibodies and cytokines
- Overproduction of proinflammatory cytokines including TNF and IL-6
- Inflammatory pathways are initiated
- Panus formation
- Proliferation of synovial cells in joints
- Cartilage destruction and bony erosion
- Manifestation of RA clinically in the form of chronic inflammation and associated symptoms

SIGNS AND SYMPTOMS

1. Articular manifestation:
2. Extra articular manifestation:
3. Systemic manifestation:

COMPLICATIONS:

Osteoporosis, Rheumatoid Nodules, Dry eyes and mouth, Infectious, Abnormal body composition, Carpal tunnel syndrome, Heart problems, Lung disease, Lymphoma

ANTI RHEUMATOID DRUGS

These are drugs which (except corticosteroid) ban suppress the rheumatoid process and bring about a remission, but do not have nonspecificanti-inflammatory or analgesic action. They are used in rheumatoid arthritis (RA) in addition to NSAIDs and are also referred to as disease modifying anti rheumatic drugs (DMARDs) or slow acting anti rheumatic drugs (SAARDs). The onset of benefit with DMARDs takes a few months of regular treatment and relapses occur a few months after cessation of therapy. Recently some Biological Response Modifiers (BRMs) have been added for resistance cases.

INTERLEUKIN-1 INHIBITORS

Interleukin-1 (IL-1) is a pro-inflammatory cytokine that plays a central role in the immune response and inflammation. It is involved in various inflammatory diseases, including rheumatoid arthritis (RA), where it contributes to joint damage and pain.
IL-1 Inhibitors are a class of drugs that block the activity of IL-1, thereby reducing inflammation and its harmful effects. By targeting IL-1, these inhibitors help manage diseases characterized by excessive inflammation.

ANAKINRA:

It is a recombinant human IL-1 receptor antagonist which competitively binds to IL receptor
Though clinically less effective than TNF inhibitors, it has been used in cases who failed on one or more DMARDS
Eg: Anakinra

MECHANISM OF ACTION:

Anakinra, a recombinant IL-1 receptor antagonist, reduces inflammation in rheumatoid arthritis by blocking the activity of IL-1α and IL-1β.

- It competitively binds to the IL-1 receptor, preventing IL-1 from binding and initiating downstream inflammatory signalling.
- This mechanism helps to control the inflammatory cascade in RA, reducing joint pain, swelling, and other symptoms

PREFORMULATION STUDIES OF PARENTRAL DOSAGE FORM:

- Preformulation studies are the early-stage research activities conducted before developing a final pharmaceutical formulation.

CLASSIFICATION OF PREFORMULATION

1.PYSICOCHEMICAL PROPERTIES:

a. Molecular weight:

- It is defined as the phase of research and development in which preformulation studies characterize physical and chemical properties of a drug molecule in order to develop safe, effective and stable dosage form.

b. Stability:

- To generate useful information on how environmental factors e.g., temperature, humidity, light etc. influence the quality of drug products over time.
- To establish the how physical, chemical and microbiological changes influence the effectiveness, safety and stability of the final drug product.
- To recommend storage conditions, establish a retest period, and shelf life of drug products.

c. Solubility:

- In preformulation studies, solubility is assessed by determining the amount of a drug or excipient that dissolves in a given solvent at specific conditions like temperature and pH.
- This involves using methods like the shake-flask method, where excess drug is added to a solvent and agitated to reach equilibrium, followed by analysis of the saturated solution.

d. Isoelectric point:

- The isoelectric point (pI), the pH at which a molecule has no net electrical charge, can be determined using isoelectric focusing (IEF) or by calculating it from the pKa values of the molecule's ionizable groups.
- IEF is a method that separates molecules based on their pI, while calculation involves averaging the pKa values of relevant groups.

2. STABILITY STUDIES:

a. Thermal stability:

- Thermal stability, the ability of a material to withstand elevated temperatures without degrading, can be checked using various methods

like thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and dynamic mechanical analysis (DMA). These methods measure changes in mass, heat flow, or mechanical properties to determine the material's thermal degradation behaviour.

b. Oxidation:

- Oxidation is caused by reaction with oxygen and is catalysed by metals, pH, and solvents. Racemization involves the loss of optical activity in chiral drugs.
- Stability can be improved by controlling pH, antioxidants, chelating agents, and solvents used

c. Ph stability:

- In preformulation studies, pH stability is checked by assessing how a drug's solubility, stability, and degradation are affected at different pH levels, mimicking the gastrointestinal tract and other biological environments.
- This helps determine the drug's stability in various conditions and inform formulation design.

3.DRUG-EXCIPIENT COMPATIBILITY STUDIES:

- This study is carried out to identify all forms of drug-excipient interactions which could alter the stability of a dosage form.
- In pharmaceutical formulations, drug substances come in direct contact with one or more excipients and therefore, can undergo chemical reactions and physical interactions under favourable conditions producing less active or inactive and toxic by-products with adverse reactions.

a. FTIR Spectroscopy:

- Fourier Transform Infrared (FTIR) Spectroscopy is a chemical analysis technique that uses infrared light to identify and quantify molecular vibrations.
- It works by passing infrared radiation through a sample and analyzing the absorbed wavelengths, creating a unique spectral fingerprint that reveals information about the sample's molecular structure.

b. DSC spectroscopy:

- Differential Scanning Calorimetry (DSC) is a thermal analysis technique that measures the heat flow into or out of a sample as it is heated or cooled. It's used to study phase transitions, chemical reactions, and changes in heat capacity of materials.
- The procedure involves comparing the heat flow of a sample to that of a reference material under controlled temperature conditions.

4. **ANALYSIS COSIDERATION**

a. HPLC:

- High Performance Liquid Chromatography (HPLC) is an analytical technique used to separate, identify, and quantify components in a liquid mixture.
- It involves injecting a sample into a column packed with a stationary phase and passing a mobile phase (liquid solvent) through the column under high pressure.
- The components in the sample separate based on their interactions with the stationary phase and the mobile phase.

b. UV Spectroscopy:

- UV spectroscopy is a technique that measures the absorption of ultraviolet (UV) and visible light by a sample to analyse its composition and properties.
- It works by passing light through the sample and measuring the amount of light transmitted or absorbed at different wavelengths.
- This allows for identification and quantification of substances based on their unique UV-Vis spectra.

5. DELIVERY CONSIDERATION:

a. Route of administration:

- The subcutaneous delivery of drugs works to balance effectiveness, convenience, and patient comfort while providing therapeutic relief
- The location of an injection is usually preferred on the thigh, stomach (around the belly button), or the upper outer arm.

b. Sterility:

- Sterility studies of injectables are crucial to ensure products are free of viable microorganisms before patient administration.
- These studies are performed using methods like direct inoculation and membrane filtration, ensuring compliance with international standards and regulations.

FORMULATION OF PARENTRAL PREPARATION:

Parenteral preparations include injection gels, implants, emulsions for injection or infusion, powders for injection or infusion, solutions, and suspensions. These are sterile preparations that are intended to be injected straight into the systemic circulation of humans or animals.

ROUTES OF ADMINISTRATION OF PARENTERAL PRODUCTS

1) Intradermal route (I.D)
2) Subcutaneous route (S.C)
3) Intramuscular route (I.M)
4) Intravenous route (I.V)

GENERAL STEPS INVOLVED IN PARENTERAL PREPARATIONS:

- Cleaning: using automatic washing and rinsing machines.
- Sterilization: Dry or moist heat.
- Purity of ingredients: drugs, vehicles, additives. For water as solvent use water for injection.
- Compounding of the preparation: Add small quantity first then larger to form solution.
- Filtration: Use Millipore membrane composed of cellulose acetate filters, for thermo-labile solutions; removes microorganisms.
- Distribution of preparation into final containers: Bottles, ampoules, plastic bags. Glass preferred since its high temperature during sterilization. Amber colored glass used for photolabile drugs but this interferes with visual inspection for foreign material.
- Closing and sealing of containers.
- Sterilization: Of filled and closed containers.
- Visual inspection for clarity.
- Labelling: Name and quantity of ingredients, storage conditions manufacturing and expiry dates.

EVALUATION OF PARENTERAL PREPARATIONS

The following tests are done to ensure that the parenteral products meet the required standards of safety and effectiveness:

- Sterility test
- Clarity test
- Pyrogen test
- Leaker test.

STERILITY TEST:

All Parenteral products should be sterile. Sterility test is performed on randomly selected samples.

Principle of the test:

A quantity of the material is transferred to a suitable liquid culture medium contained in a tube. A number of culture media are used:

- Thioglycolate liquid medium: used to support the growth of anaerobic organisms. It is incubated for 7 days at 35 - 37 C.
- Soybean-casein liquid medium: to support the growth of aerobic organisms. It is incubated for 7 days at 35 - 37 C.

Observations of the sterility test:

The tested material is sterile if no growth or turbidity in a, b, c, g, while d, e, f, show growth. If growth observed in a, b, c, g, or no growth in d, e, f, the test should be repeated with fresh sample. If there is growth repeat test. If still there is growth, then preparation is unsterile and is rejected.

PYROGEN TEST:

Pyrogens are metabolic products which are produced by all microorganisms from their cell wall. They consist of liposaccharide and they are water soluble, filterable and thermostable. They are not removed after sterilization by moist heat or filtration. In the human body they cause febrile reaction (fever, headache, backache) [22]. Major source of pyrogens is water which is used as a vehicle. Pyrogens can be removed by adding oxidizing agent (potassium permanganate + small quantity of barium) to oxidize pyrogens to non-volatile organic solids (filterable). It is performed on all aqueous parenteral preparations. Rabbits are used for the test since they show same response to pyrogens as humans.

CLARITY TEST

Clarity is defined as the freedom of parenteral preparations from any foreign matter. The clarity of solutions is visually inspected under strong light.

LEAKER TEST

This test is specific for ampoules to test that they are effectively sealed with no leak. The clarity test for injections is a visual inspection performed to ensure that parenteral solutions are clear, free from visible particles, and suitable for safe administration. Conducted under standardized lighting against black and white backgrounds, the test helps detect any particulate matter, cloudiness, or discoloration in the solution. It follows pharmacopeial standards such as USP <790> and EP 2.9.20, and may be done manually or with instruments for detecting sub-visible particles. A solution passes the test if it appears clear and free from any visible contamination or precipitation.

Steps:

- The ampoules are immersed in a tank containing dye solution (1% methylene blue).
- The tank is closed and the air inside is evacuated to form negative pressure inside the tank [23]. The vacuum will create high pressure on the weak points on the ampoule seal and will also assist the passage of the dye into the leaking ampoule.
- The ampoules are washed and any leaking one will contain the blue dye and should be rejected.

PROCESS FOR STERILIZATION OF PARENTRAL PRODUCTS:

1. Autoclave sterilization: Usually to sterilize by autoclave a pressurized steam autoclave operates at 121ºC for at least 15 min.
2. Radiation sterilization: This method is very important for medical devices. That can withstand the attack of gamma rays' bombardment. Radiation sterilization is only useful for the polymers which are sensitive to heat moisture or ethylene oxide.
3. Gas sterilization: Ethylene oxide is generally used as sterilant. It is nontoxic to most plastics. Ethylene oxide sterilization is used for most of the plastic syringe and needles.

INDUSTRIAL DOCUMENTATION OF ANAKINRA INJECTION

1. PRODUCT INFORMATION FILE (PIF)
2. MASTER FORMULA RECORD (MFR)
3. BATCH MANUFACTURING RECORD (BMR)
4. BATCH PACKAGING RECORD (BPR)
5. ANALYTICAL AND QUALITY CONTROL RECORDS
6. STERILITY ASSURANCE AND ASEPTIC PROCESSING RECORD
7. DEVIATION & CAPA DOCUMENTATION (IF APPLICABLE)
8. STABILITY STUDY DOCUMENTATION
9. REGULATORY DOCUMENTATION
10. FINAL PRODUCT RELEASE RECORD

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