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"A REVIEW ON EXPERIMENT ANIMAL MODELS OF RHEUMATOID ARTHRITIS"

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Abstract-**Rheumatoid arthritis (RA) is a continual inflammatory and systemic car immune sickness - human beings predominantly among the a while of 20-50 years with unpredictable course. About 1% of the world's population is afflicted by rheumatoid arthritis and is two to three times more common in women than men. There are different types of arthritis. The rheumatoid arthritis due to the presence of pro-inflammatory markers, cytokines and leukotrienes. There are distinct animal fashions are used to set off arthritis in rats to assess the anti-arthritic activity. The selection of appropriate animal models depends on two important criteria- morphological similarities with human RA and capacity to predict efficacy of various drugs in human. The prompted fashions have been advanced to expect the efficacy of anti-arthritic tablets whilst genetic fashions have been advanced to assess the development of sickness kingdom in animals with an intention to set up a correlation with human RA in each cases. These fashions in addition permit predicting the toxicities which arise at better doses or at some stage in extended dosing period. Although, diverse animal fashions emphasis the validated relevance to human rheumatoid arthritis.**

Keyword: Rheumatoid arthritis, animal models, Freunds Adjuvant Induced.

INTRODUCTION

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is chronic, systemic autoimmune disorder that is associated with symmetrical, inflammatory polyarthritis that may produce progressive joint damage. Inflammation of the joint tissues is associated with the release of toxic substance in the synovium that leads to cartilage destruction. NSAIDS, Biologic Response Modifiers and Corticosteroids are the most commonly used drugs for the treatment of RA. However, all of those dealers are related to severa aspect effects. In present days, investigators are conducted towards traditional system of medicine for the exploration of drugs that are long acting anti-inflammatory with minimal side effects. The arthritis-like signs in AA rats proportion numerous histopathological capabilities with human RA, together with mononuclear mononuclear cell infiltration and synoviocyte hyperplasia that outcomes in pannus formation observed with the aid of using bone and cartilage destruction. The similarities in the joint pathology between rat arthritis and human RA are most widely used for studying the pathogenesis of human PA and for searching new drugs for RA management. Therefore, AA is most frequently used as a model for screening and testing anti-arthritic agents.[1]

RA is a complicated process, regarding synovial mobileular proliferation and fibrosis, pannus formation and cartilage and bone erosion. This system is mediated through an interdependent community of cytokines,

prostanoids and proteolytic enzymes. Proinfalmmatory cytokines, together with interleukin-1 (IL-1) and tumor necrosis factor (TNF-α), are crucial mediators in RA. This is illustrated in sufferers with RA, who enjoy an preliminary cell-mediated reaction that results in the presence of accelerated tiers of IL-1 withinside the synovial fluid. Furthermore, IL-1 concentrations withinside the plasma had been stated to correlate with ailment activity. It has additionally been established that sufferers with erosive RA have better synovial and circulating ranges of IL-1 than sufferers with out erosions. Interleukin-6 (IL-6) is an inflammatory cytokine that is characterized by pleiotropy and redundancy of action, involved in inflammation, bone metabolism, immunity, endocrine functions and in particular it is a principal regulator of the synthesis of acute segment reactants with the aid of using the liver. IL-6 is produced via way of means of many distinctive cells withinside the frame consisting of lymphocytes, monocyte, fibroblasts and endothelial cells. Adipose tissue is another major source of IL-6, accounting for about 30% of total circulating concentrations of IL-6 in healthy subjects. Excessive adipose tissue deposition ends in immoderate manufacturing of IL-6, a excessive danger aspect to the RA. Body mass index (BMI) is a longtime threat thing for knee osteoarthritis (OA). Weight loss can help to reduce the incidence of symptomatic knee OA. [2]

GENERAL CONSIDERATION OF ARTHRITIS

RA can be classified as

1. Palindromic rheumatoid arthritis
2. Juvenile rheumatoid arthritis
3. Rheumatoid spondylitis
4. Other types of arthritis
5. Osteoarthritis

There are two types of osteoarthritis –

A) Primary osteoarthritis - It happens in elderly.

B) Secondary osteoarthritis- It happens at any stage.

- Ankylosing spondylarthritis
- Infectious arthritis
- It can be classified as fallows

a) Supportive arthritis

b) Tuberculous arthritis

c) Lyme arthritis

d) Viral arthritis

DIAGNOSIS

Diagnosis for RA includes using scientific strategies of imaging and laboratory tests. Laboratory trying out strategies encompass anaemia, presence of rheumatoid factor, antibodies in opposition to the cyclic citrullinated peptides and elevation in erythrocyte sedimentation rate. While symptomatic detection of stiffness and pain for a long time in the morning gives some clue about the disease. X-rays additionally assist in detecting the RA however at instances they can't differentiate in early arthritis too. MRI and ultrasounds also are carried out to study the development of the RA withinside the patients. No such highly specified test has been developed for validation of the disease. [3-4]

EPIDEMIOLOGY

The prevalence of rheumatoid arthritis (RA) varies between 0.3% and 1% worldwide and is more in developed countries.

- It mainly affects women than men (3:1).

Generally, it moves among 30 and fifty five years. It affects 0.5-1.0% of adults, Rheumatoid arthritis (RA) is a chronic systemic inflammatory illness with prevalence of approximately 0.75% in India [5]

ETIOLOGY

The etiology of RA continues to be now no longer known, a genetic susceptibility in aggregate with the affect of environmental elements are in all likelihood conditions for the onset of RA. The factors are[6]:

- Environmental factors
- Impact of sex and sex hormones
- Genetic factors

SYMPTOMS

Symptoms of arthritis are gradually developed. The first signs and symptoms are frequently felt in small joints, i.e. palms and toes, despite the fact that shoulders and knees may be affected early, and muscle stiffness may be a distinguished early feature

- Symptoms of RA includes
- Morning stiffness that last for at least 1 hr.
- Joint pain with warmth, swelling, tenderness and stiffness of the joint after resting
- Low-grade fever.
- Inflammation of small blood vessels can cause small nodules under the skin, but they are generally painless.

ANIMALS

Adult albino rats of Wistar strain weighing 120 - 175 g and adult Albino mice were used in the pharmacological and toxicological studies. The animals had been maintained in properly ventilated room temperature with herbal 12 ± 1 h day–night time cycle withinside the propylene cages. The protocol was approved by Animal Ethics Committee constituted for the purpose as per CPCSEA Guideline. [7]

INDUCTION OF ARTHRITIS IN ANIMAL MODELS

1. Complete Freunds Adjuvant Induced (CFA) Arthritis in Rats.

Freund's entire adjuvant brought on arthritis in rat version is the first-class and maximum extensively used experimental version for arthritis. It is a T cell and neutrophil dependent and complement independent helper (Th) 1 and (Th) 17 inflammatory cytokines are associated CFA induced arthritis. Increased levels of TNFα, interferon γ (INFγ), IL1, IL6 and IL17A mRNA have been detected in this type of model. This model is sensitive to anti inflammatory and immune inhibiting medicines and best for the study of phathophysiological and pharmacological control of inflammation process as well as for the evaluation of anti-nociceptive potential of drug. AIA is not joint-specific but is associated with granuloma formation in various organs and tissues, such as the spleen, liver, bone marrow, skin and eyes. [12-13]

Procedure

Animals are randomly divided into five groups of six animals. Group I served as managed obtained everyday saline. Standard and test groups are further divide into two sections of treatment i.e. Prophylactic (P) group (before induction of disease) and therapeutic (T) group (after induction of disease). Group II and Group III

were standard group received Indomethacin (10 mg/kg p.o), Group IV and V were test group received the test drug. On day zero animals are injected into the sub plantar region of the left hind paw with 0.1 ml of complete Freund's adjuvant (FA). This consists of 6mg Mycobacterium butyric suspended in heavy paraffin oil by through grinding with mortor and pestle to give a concentration of 6 mg/ml. Drug remedy is began out from the 14th day i.e. from the day of adjuvant injection and continued till 28thday. The paw oedema and joint thickness is measured on 7th, 14th, 21stand 28thday via way of means of the usage of virtual verniercallipers or plethysmometer. The mean changes in injected paw oedema and joint thickness with respect to initial paw volume and joint thickness, are calculated on respective days and % inhibition of paw oedema and joint thickness with respect to untreated group are calculated using following formula. Inhibition in paw edema / joint thickness = 100 x (1- Vt/ VC) VC = Mean paw edema volume/ joint thickness in control group VT = Mean paw edema volume/ joint thickness in the drug treated group In radiological analysis, radiographs are taken by using X-ray apparatus. X-rays are taken on the joint of hind paw of the animal for comparing the bone harm earlier than sacrificing the animal. In histopathological analysis, the ankle joint of rats are eliminated and separated from the encircling tissues. To examine the histopathological changes during the experimental period in all the groups under the light microscope, the joints are fixed in 10 %formalin and decalcified, sectioned and finally stained with eosin and hematoxyline. [14-15]

2. Formaldehyde-induced arthritis

Principles

Swelling in the ankle joints and around the feet of arthritis is believed to be caused by edema of tissues such as ligaments and joint capsules22. Edema in rat paws after formaldehyde injection is due to the release of histamine, serotonin and prostaglandin-like substances at the injection site 2. Formaldehyde triggers arthritis by denaturing proteins at the application site, thus creating an immune system against product degradation. [17]

Method

Animals were divided into four groups of six animals each, the first group was given control and 0.5% CMC, the second group was given indomethacin (10 mg/kg orally) Standard products, Group III and IV were tested. He took his medicine. On the first and third day of the experiment, 0.1 ml of formaldehyde solution was injected into the plantar region of the mouse's left hind paw. Tests and samples were administered orally once a day for 10 days. Rat paw thickness was measured daily for 10 days. Current inhibition of the increase in paw edema was calculated at day 10 for each group and compared with the control group. Measure paw edema using a digital vernier caliper or plethysmograph. [18]

3. Type II collagen-induced arthritis (CIA) in rats

PRINCIPLE

The CIA model is an animal model of RA. It is complement dependent. Three different cartilage-derived proteins are responsible for inducing arthritis in mice; namely collagen type II, collagen type XI and cartilage oligomeric matrix protein. It is a good model to study immune mechanisms against autoantigens that are frequently involved in human diseases. Collagen arthritis is induced in various mouse strains by injection of type II collagen emulsified in Freund's incomplete adjuvant (IFA). After induction of the disease, cellular and humoral immunity is established against type II collagen, which can be passively propagated by susceptible spleen and lymph node cells and IgG antibodies against type II collagen. Collagen arthritis is an immune response to type II collagen. Once in the dermis, type II collagen is immediately captured by antigen-presenting cells (APCs). In this type of disease, activation of T and B cells is antigen-specific and autoreactive. T cells and T cell-derived cytokines promote the differentiation and activation of macrophages, osteoclasts, and fibroblasts, leading to the development of aggressive erosive arthritis. 18 CIA is genetically controlled by the expression of class II major histocompatibility complex (MHC) molecules, specifically I-Aq and I-. Ar in mice. [12]

Program

Dissolve type II collagen in 10 mM (4 mg/ml) acetic acid at 4°C overnight. This solution is then emulsified in an equal volume of chilled Freund's complete adjuvant and mixed with a homogenizer at 1000 rpm for 30 minutes. Arthritis was induced by subcutaneous injection of 100 µl of emulsion (BnCII 100 mg + CFA 100 mg) into the paw root. On day 7 after the first injection, mice were stimulated with the same volume of emulsion intradermally at the base of the tail. Control animals received only Freund's complete adjuvant diluted in 10 mM acetic acid. Oral indomethacin (10 mg/kg) was administered during the procedure. Methods and experimental groups started drug treatment on the 18th day after infection and continued until the 36th day. The volume of both ridges was measured by plethysmography. [19]

4. Pristane-Induced Arthritis (PIA)

Rat PIA is a chronic, parallel inflammatory model that mimics many human diseases. Mineral oil pristane was used to induce PIA in injured rats. Symptoms of the disease begin to appear after 7-10 days. The experiment can be terminated approximately 30 days after induction. PIA is T cell driven and MHC dependent, but no antibodies have been identified in PIA to date. This virus can also be transmitted by T cells, allowing direct examination of T cell arthritogenicity ex vivo. [20]

Pristane-induced arthritis (PIA) is a preclinical arthritis model that displays features of human rheumatoid arthritis (RA) such as symmetric inflammation, chronic and relapsing, T cell infiltration, and erosive damage to cartilage peripheral joints. It is frequently used to evaluate the mechanisms of joint diseases and to test the results of new arthritis treatments. Methods

Arthritis was induced by intradermal injection of 150 µl of the original drug (2,6,10,14-tetramethylpentadecane) into the base of the tail. Sensitized mice showed an immediate onset of severe arthritis within 2 to 3 weeks after pristane injection. Arthritis was performed in all mice at 8–12 weeks of age. point for moderate foot and ankle swelling, and 5 points for ankle swelling). . Scores for the four paws were calculated to give a maximum of 60 points for each rat. After pristane injection, mice were observed 1 to 4 times per week for 28 days.

Due to the production of autoantibodies, this model can be used to model lupus erythematosus (SLE). To understand the different causes of autoimmunity, studies are needed to identify genes involved in the development of arthritis and autoantibody production. [21]

5. Oil-induced arthritis (OIA)

OIA occurs approximately 14 days after intradermal injection of IFA. In these cases, monoarthritis occurs in the hind paws and ankles and can also extend to the front paws. Disease resolution on the 45th day[22]

6. Streptococcus Cell Wall Induced Arthritis

Aqueous suspensions of cell wall peptidoglycan-polysaccharide fragments of Streptococcus and several other bacteria, given as intraperitoneal injection into an infected mouse (male Lewis rats), can induce arthritis. The painful, thymus-dependent, supplement-dependent phase develops within 24 hours. [23]

Purified peptidoglycan-polysaccharide (PG-PS) polymer produced by Streptococcus pyogenes has the capacity to cause liver and arthritis in mice. Depending on the PG-PS material and application method, two types of arthritis can occur. These models are rarely used in clinical trials, perhaps due to their high cost. However, SCW-induced arthritis has the advantage of the AIA model because the SCW model can examine acute or ictal responses to arthritis. [24]

The two models are as follows:-

- Polyarticular SCW-induced arthritis

The polyarticular model is induced by intraperitoneal (IP) injection of live PG-PS 10S into susceptible strains. pain. inflammatory reactions and joint swelling. The combination of pain in the first 5 days and then from the

time it is allowed results in chronic arthritis. This model provides an opportunity to study the early and long-term stages of arthritis. [25]

- Single-joint SCW-induced arthritis

In this model, intra-articular injection of PG-PS 100P into the stretch-sensitive posterior ankle joint causes a primary inflammatory surge. This resolves within a few days, leaving a significant synovial infiltrate in the joint containing lymphocytes and mononuclear cells. After the first intra-articular injection, the joint will become tender and injection of PG-PS 100P, lipopolysaccharide or superantigen can relieve pain in the joint. The single-joint SCW-induced arthritis model appears to be mediated by Th2 cells, as inflammation of this model occurs within hours. It has been reported that IL-4 is important in the development of the disease, while blocking IFNγ and IL-10 does not affect the relationship.

IL-1, TNF and IL-4 play an important role in the SCW-induced arthritis model. The combination of IL-4 and TNF potentiates T cell adhesion molecules, thereby potentially ameliorating the transition period of T cell-mediated inflammation. Chemokines such as CCL2/MCP-1, MIP-1, and MIP-2 all play a role in the response after RA reactivation. The single-joint SCW-induced arthritis model is suitable for studying the effects of treatment over time because it simulates arthritis-like conditions occurring in RA patients. Additionally, because the disease is less severe than other types of arthritis, animals can be monitored for longer periods of time. Importantly, the expression of cytokines such as IL-1β, IL-6, and TNF-α indicates that the best time to evaluate the clinical effect is 3 days after injection. [26]

7. Septic arthritis caused by Staphylococcus aureus

To induce arthritis, a suspension of live bacteria (Staphylococcus aureus) was injected into the tail muscle of each mouse. The clinical score (arthritis index) was used to assess arthritis pain as previously described. [27]

CONCLUSION

Rheumatoid arthritis is an autoimmune disease known to cause deformity and pain due to pain in the patient's joints.

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