Arthritis an autoimmune disorder: Demonstration of In-vivo anti-arthritic activity

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Abstract

In the normal knee joint, the synovium consists of a synovial membrane (usually one or two cells thick) and underlying loose connective tissue. Synovial-lining cells are designated type a (macrophage-like synoviocytes) or type B (fibroblast-like synoviocytes). Arthritis is an auto immune disorder characterized by pain, swelling and stiffness. Its prevalence depends upon age. It occurs more frequently in women than in men. It is an inflammation of synovial joint due to immuno mediated response. All anti inflammatory drugs are not anti arthritic because it does not suppress T-cell and B-cell mediated response. For evaluation of anti arthritic drugs inflammation and T-cell and B-cell mediated response by including foreign antigen should be suppressed. The high incidences of anti-CII antibodies and CII-specific T cells indicate that CII is one of the major auto antigens of human RA. In this way, the higher prevalences of CII-specific antibodies and T cells noted during the early phase of RA indicate that CII-specific immunity plays an important role in the initiation of inflammation in the articular joints. So, collagen type-II is best model for evaluation of anti-arthritic drugs compare to other models.

Keywords: Arthritis, synovial joint, synoviocytes, auto antigens

Introduction

Arthritis is an auto immune disorder characterized by pain, swelling and stiffness. Its prevalence depends upon age. It occurs more frequently in women than in men. It is an inflammation of synovial joint due to immuno mediated response. All anti inflammatory drugs are not anti arthritic because it does not suppress T-cell and B-cell mediated response. Rheumatoid arthritis (RA) is an autoimmune disorder characterized by synovial proliferation, inflammation, subsequent destruction like deformity of joints or destruction of cartilage and bone[1]. RA is the most common inflammatory joint disease in humans, has long been classified among the autoimmune diseases in which Skeletal complications start with focal erosion of cartilage followed by marginal and subchondral bone loss. Extended joint destruction with ankylosis and generalized bone loss are characteristic for late complications[2]. These long-term skeletal complications have serious consequences as they can lead not only to painful joint deformities but also to progressive functional disability and increased mortality rates[3].

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Epidemiological Study

Women it rose up to the age of 45 plateaued to 75. Epidemiological studies overall show a female to male ratio of about 3:1[4]. But this all class of drugs is responsible for symptomatic relief. To evaluate the drug which actually prevent cause of arthritic or act during various step of arthritis there is requirement of evaluative model which produce arthritis in animal same that produce in humans. Animal models of arthritis are used to study pathogenesis of disease and to evaluate potential anti-arthritic drugs for clinical use. Therefore morphological similarities to human disease and capacity of the model to predict efficacy in humans are important criteria in model selection[5].

Pathophysiology of arthritis

In the early stages of rheumatoid arthritis, the synovial membrane begins to invade the cartilage. In *established RA*, the synovial membrane becomes transformed into inflammatory tissue, the *pannus*. This tissue invades and destroys adjacent cartilage and bone. The interface between pannus and cartilage is occupied predominantly by activated macrophages and synovial fibroblasts that express matrix metalloproteinases and cathepsins. IL-1 and TNF-α stimulate the expression of adhesion molecules on endothelial cells and increase the recruitment of neutrophil into the joints. Neutrophil release elastase and proteases, which degrade proteoglycan in the superficial layer of cartilage [6,7]. The depletion of proteoglycan enables immune complexes to precipitate in the superficial layer of collagens and exposes chondrocytes[8].Chondrocytes and synovial fibroblasts release matrix metalloproteinase (MMPs) when stimulated by IL-1, TNF-α, or activated CD4+ T cells. MMPs, in particular stromelysin and collagenases, are enzymes that degrade connective-tissue matrix and are thought to be the main mediators of joint damage in RA. In animals, activated CD4+ T cells stimulate osteoclastogenesis, and they may cause joint damage independently of IL-1 and TNF-α in patients with RA.
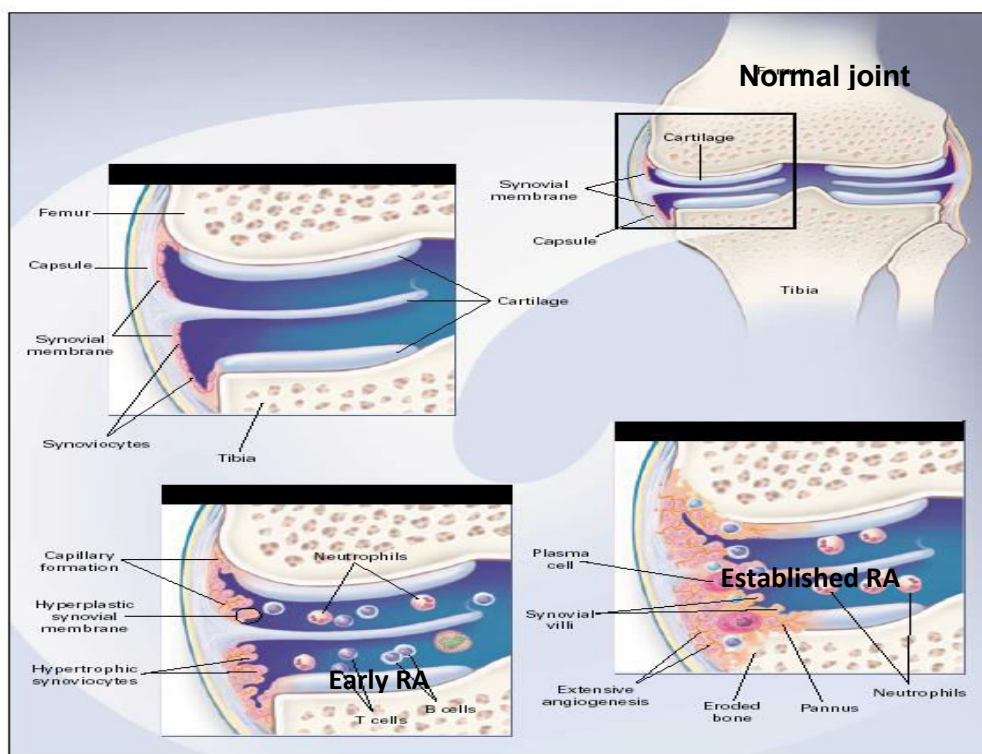
Fig1: Describe pathophysiology of rheumatoid arthritis

Evaluation of Antiarthritic parameter is that it gives sympathetic relief main prevent Inflammation and pain. So the must posses Analgesic, Anti inflammatory property, arthritis is immune. So drug should be immune modulators. For that parameters Antiarthritic activity is evaluate. Joint fluid evaluation Baseline evaluation of renal and hepatic

function also is recommended because these findings will guide medication choices[9]. on their guideline various experimental parameters are create to anti –arthritic activity in animal like , Paw edema, Body weight,Arthritic index, Erythrocyte Sedimentation Rate (ESR), Quantitative determination of the Rheumatoid Factors (RF),Histopathology of synovial joints, Radiology (x-Ray measurements),Photographic parameter

a) Paw edema:
Paw volumes of both hind limbs are record on the day of arthritis induction, and again measured on day first; third, fifth, ninth, up to last day of experiment using mercury column plethysmometer.on last day of experiment rheumatoid arthritis becomes more evident and inflammatory changes spreads systemically and becomes observable in the limb not inducted with arthritis [10].

Arthritic Index: All the animals are closely observed for organs like ears, nose, tail, fore paws and hind paw and arthritic index (Pearson CM, 1959) was calculated [11].

Erythrocyte Sedimentation Rate (ESR): The westergren method is use for measurement of ESR[12].

Reumatoid Factor: The latex turbidimetry method is use in the present study using RF turbilatex kit. Calibration is carried out for linear range up to 100 IU/ml. The reading of RF factor of all the groups obtained is compare with the control animals and is express as IU/ml RF [13].

Histopathology of Synovial Joints: The synovial joint is isolated for the biopsy examination of synovium proliferation, synovial lining angiogenesis, and rheumatoid inflammation. This destruction was separately graded on a scale from 0 to 3, ranging from no abnormalities to complete loss of cortical and trabecular bone of the femoral head. Cartilage and bone destruction by pannus formation was scored ranging from 0, no change; 1, mild change (pannus invasion within cartilage); 2, moderate change (pannus invasion into cartilage/subchondral bone); 3, severe change (pannus invasion into the subchondral bone); and vascularity (0, almost no blood vessels; 1, a few blood vessels; 2, some blood vessels; 3, many blood vessels) [14-17].

Radiography: Radiographs are carefully examined using a stereo microscope and abnormalities are grade as follows: periosteai reaction, 0-3 (none, slight, moderate, marked); erosions, 0-3 (none, few, many small, many large); joint space narrowing, 0-3 (none, minimal, moderate, marked); joint space destruction, 0-3 (none, minimal, extensive, ankylosis). Bone destruction was scored on the patella as described previously [17, 18].

Experimental arthritis: a few examples of animal models

Many animal models of RA are available. Early models were intended for investigating etiological hypotheses or conducting pharmacological studies (Table 1).

Immune arthritis	Intraarticular antigens, Adjuvants, Collagen type II, Streptococcal wall, Pristane
Infectious arthritis	Retrovirus, Erysipelothrix, Chlamydiae, Mycoplasmas (M. arthritidis),
Chemical arthritis	Macromolecules (dextran, carrageenan)

Rat models of erosive arthritis can be classified into three major groups (I) Arthritis induced by hyperimmunization type II collagen (collagen-induced arthritis) or cartilage oligomeric matrix protein (COMP-induced arthritis) in incomplete Freund"s adjuvant (IFA).(II) Arthritis induced by oil-based adjuvants e.g. Mtb-adjuvant-induced arthritis, avridine- induced arthritis, pristane , pristane-induced arthritis.(III) bacterial cell wall peptidoglycan polysaccharide-induced arthritis e.g. streptococcal cell wall (SCW) arthritis model, pristane-induced arthritis (PIA) and proteoglycan-induced arthritis[19,20].

Comparison of rat and mouse models of erosive arthritis to rheumatoid arthritis (RA) in humans (Table 2)

Model	Similarities to human disease	Differences from human disease
Collagen-induced arthritis (CIA) in rats	Symmetrical joint involvement, peripheral joints affected, persistent joint inflammation, synovial	Anti-collagen responses not present in many cases of RA

	hyperplasia, inflammatory cell infiltration, marginal erosions, presence of Rheumatoid Factor and anti-collagen antibodies, genetically regulated by MHC and non-MHC genes, responsive to most therapies effective in RA	
Adjuvant-induced arthritis (AIA) in rats	Symmetrical joint involvement, peripheral joints affected, persistent joint inflammation, synovial hyperplasia, inflammatory cell infiltration, marginal erosions, genetically regulated by MHC and non-MHC genes, and responsive to most therapies effective in RA	Rapid explosive onset of highly erosive polyarthritis, monophasic course, involvement of axial skeleton, No Rheumatoid Factor, gastrointestinal, genitourinary tract and skin affected; periostitis, bony ankylosis extra-articular manifestations not typical of RA.
COMP-induced arthritis in rats	Symmetrical joint involvement, peripheral joints affected, persistent joint inflammation, immune responses to proteins in the cartilage, genetically regulated by MHC and non-MHC genes	No permanent destruction of joints, transient disease
Proteoglycan-induced arthritis in mice	Symmetrical joint involvement, peripheral joints affected, persistent joint inflammation, synovial hyperplasia, inflammatory cell infiltration, marginal erosions, presence of Rheumatoid Factor and circulating auto antibodies to collagen type II, deposition of immune complexes, genetically regulated by MHC and non-MHC genes	Development of spondylitis
Streptococcal cell wall-induced arthritis	Symmetrical joint involvement, peripheral joints affected, persistent and relapsing joint inflammation, synovial hyperplasia, inflammatory cell infiltration, marginal erosions, greater disease susceptibility in females, genetically regulated by MHC and non-MHC genes	No Rheumatoid Factor in rats
Carragenan induce arthritis	Symmetrical joint involvement, peripheral joints affected, persistent joint inflammation, synovial hyperplasia, inflammatory cell infiltration, marginal erosions, presence	No evidence of immune response.

The putative mechanisms have evolved as our immunologic knowledge has expanded, and have varied with the trends in immunology. Throughout these developments in understanding human RA, animal models have played a key role in

defining mechanisms. Collagen-induced arthritis is an extensively studied animal model of RA because it shares both immunological and pathological features of human RA. CIA is primarily an autoimmune disease of joints, requiring both T and B cell immunity to autologous type II collagen (CII) for disease manifestation[19, 20].

Conclusion

For evaluation of anti arthritic drugs inflammation and T-cell and B-cell mediated response by including collagen type-II (bovine collagen). This foreign collagen produces auto immune response. Type II collagen as an auto antigen in human RA and collagen-induced arthritis (CIA), Most autoimmune diseases involve the development of autoimmunity to autologous proteins and have been probed for auto reactive T cells and antibodies in both human disease and animal models. The high incidences of anti-CII antibodies and CII-specific T cells indicate that CII is one of the major auto antigens of human RA. In this way, the higher prevalence's of CII-specific antibodies and T cells noted during the early phase of RA indicate that CII-specific immunity plays an important role in the initiation of inflammation in the articular joints. So, collagen type-II is best model for evaluation of anti-arthritic drugs compare to other models.

References

1. Firestein G.S. (2003). Evolving concepts of rheumatoid arthritis. *Nature*, 356–61.

2. Feldmann M., Brennan F.M. and Maini R.N. (1996). Rheumatoid arthritis. *Cell*, **85**: 307–310.

3. Pincus T. and Callahan L.F. (1993). The side effects of rheumatoid arthritis: joint destruction, disability and early mortality. *Br. J. Rheumatol*, **32 (Suppl 1)**: 28–37.

4. Lawrence J.S. (1961). Prevalence of rheumatoid arthritis, *Ann Rheum Dis*, **20**: 11-17.

5. Goldring S.R. and Gravallese E.M. (2000). Mechanisms of bone loss in inflammatory arthritis: diagnosis and therapeutic implications. *Arthritis Res*, **2**: 33–37.

6. Rang H.P., Dale M.M., Ritter J.M. and Moore P.K. (2006). *Pharmacology*, 5th edition Charchill Livngstone, New Delhi, 244-260.

7. Moore A.R., Lwamura H., Larbre J.P., Scott D.L. and Willoughby D.A. (1993). Cartilage degradation by polymorphonuclear leucocytes : in vitro assessment of the pathogenic mechanisms. *Ann Rheum Dis*, **52**: 27-31.

8. Jasin H.E. and Taurog J.D. (1991). Mechanisms of disruption of the articular cartilage surface in inflammation: neutrophil elastage increases availability of collagggen tye II epitopes for binding with antibody on the surface of articular cartilage. *J Clin Invest*, **87**: 1531-1536.

9. Saraux A., Berthelot M., Chales G., Le Henaff C., Thorei J.B. and Hoang S. (2001). Ability of the American College of Rheumatology 1987 criteria to predict rheumatoid arthritis in patients with early arthritis and classification of these patients two years later. *Arthritis Rheum*, **44:2485**-2491.

10. Colpert K.M. (1987). Evidence that adjuvant arthritis in the rat is associated with chronic pain. **28**: 201-222.

11. Pearson C.M., Wood F.D. (1959). Studies on polyarthritis and other lesions induced in rats by injection of mycobacterium adjuvant. I. General clinic and pathological characteristics and some modifying factors, *Arth rheum*, **2**:440-459.

12. Goyal R.K. and Patel N.M. (2008). *Practical Anatomy & Physiology*, 11th edition, B.S.Shah Prakashan Ahmedabad, 34-36.

13. Van de Berg W.B., Joosten L.A.B., Helsen M.M.A. and Van de Loo F.A.J. (1994). Amelioration of established murine collagen-induced arthritis with anti-IL-1 treatment. *Clin Exp Immunol*, **95**:237–243.

14. Joosten L.A.B., Lubberts E., Helsen M.M.A. and Van den Berg W.B. (1997). Dual role of IL-12 in early and late stages of murine collagen type II arthritis. *J Immunol*, **159**:4094–4102.

15. Taniguchi K., Kohsaka H., Inoue N., Terada Y., Ito H., Hirokawa K. and Miyasaka N. (1999). Induction of the p16INK4a senescence gene as a new therapeutic strategy for the treatment of rheumatoid arthritis. *Nat Med*, **5**:760-767.

16. Robert H. Shmerling (1991). The Americn Journal of Medicine, 91:528-534.

17. Joosten L.A.B., Helsen M.M.A., Van de Loo F.A.J. and Van den Berg W.B. (1996). Anticytokine treatment of established collagen type II arthritis in DBA/1 mice: a comparative study using anti-TNF alpha, anti-IL-1 alpha, beta and IL-1Ra. *Arthritis Rheum*, **39**:797–809.

18. Salvatore Cuzzocrea, Emanuela Mazzon, Rosanna Di Paola, Carmelo Muia, Concetta Crisafulli, Laura Dugo, Marika Collin, Domenico Britti, Achille P. Caputi and Christoph Thiemermann (2006). Clinical Glycogen synthase kinase-3b inhibition attenuates the degree of arthritis caused by type II collagen in the mouse. *Immunology*, **120**: 57—67.

19. Van Eden W., Van der Zee R., Taams L.S., Prakken A.B., Van Roon J. and Wauben M.H., (1998). Heat-shock protein T-cell epitopes trigger a spreading regulatory control in a diversified arthritogenic T-cell response. *Immunol Rev*, **164**:169–74.

20. Wilder R.L. (1999). Genetic factors regulating experimental arthritis in mice and rats, In *Current Directions in Autoimmunity* (Theophilopoulos, A.N., ed.), 121-165.