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PATHOLOGICAL RESEARCH APPREHENSION OF AMAVATA W.S.R. TO RHEUMATOID ARTHRITIS

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ABSTRACT

Amavata (Rheumatoid arthritis) is a chronic, systemic autoimmune disorder associated with inflammation and tissue damage in joints (arthritis) and tendon sheaths. In Ayruvedic context, abnormal *Aama* and *Vata* are the important predisposing factors. First time, *Madhav nidana* mentioned *Amavata* as separate disease. After that *vangsena, chakaradutta, bhaishjya ratnavali* has elaborated the treatment modalities of *Amavata*. Ayurveda focus on *Nidaan* i.e cause of disease and symptoms of disease. Ayurveda says *chikitsa* (Treatment) is *Nidaan Parimarjna*(removal of cause). Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily affects the lining of the synovial joints and is associated with progressive disability, causes swelling, pain and stiffness of joints. Chronic condition may cause debility, deformities of joints and crippling. When cause of disease is unknown then how a physician can provide proper treatment. This study has focus on nidaan (causative factors), *Samprapti* (Pathogenesis) and *Sadhyata/ Asadhyata* (Prognosis) of disease *Amavata* with special reference to RA. So this study will help scientific society to understand RA pathogenesis, disease modifying drugs, and provides perspectives on therapeutics for RA.

KEYWORDS: *Aamvaat*, Rheumatoid arthritis, Immunomodulatory, Pathogenesis.

INTRODUCTION

Amavata (Rheumatoid arthritis) is prevalent worldwide in all races, sexes, age and climates. It is a chronic, systemic autoimmune disorder associated with inflammation and tissue damage in joints (arthritis) and tendon sheaths. If left untreated the disease affects the systems of the body and worsen the life. The etiology of this disease is unknown and predisposing factors are improper food habits and life styles.[1]

This disease is termed as "*Amavata*" in Ayurveda. The word '*Ama*' means to toxic unwholesome product, which is produced in the body due to weakening of digestive fire. This '*Ama*' is then carried by '*Vayu*' and travels through the channels of the body and accumulates in the joints, which is the seat of '*Kapha*. As this process continues, all the joints are gradually affected resulting in severe pain and swelling in the joints. When '*Pitta*' gets aggravated, it causes burning sensation around the joints.[2,3]

Since the disease has auto-immune factor and persistent inflammation, the drugs which possess immunomodulatory and anti-inflammatory property are best suited. Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that arises more frequently in females than males, being predominantly observed in the elderly. The prevalence rate reported in 2022 ranged from 1% to 3% of the population and had regional variation.[4] RA primarily affects the lining of the synovial joints and can cause progressive disability, premature death, and socioeconomic burdens. Unfortunately the man has not succeeded in eradicating this diseases and find to come out with successful therapeutic measures that can cure the patient completely. The diagnostic capability of the physician all influence the treatment and outcome of RA.

REVIEW OF LITERATURE

Cause or *nidana* of *amavata*

Nidana is defined as the factors which deranges the dynamic state of *doshik* equilibrium provokes the disease is known as *Nindan*. This *Nidana* helps us to decide the line of treatment as well as prognosis of the disease. *Amavata Nidan* is of multifaceted various Acharya's mentioned their different views for the productions of *Ama* in *Amavata*. Madhavakara[5] told the separate *Nidana* as-

Viruddha Ahara (Incompatible food)
Viruddha Chestha (Incompatible actions)
Mandagni (Hypo functioning of *agni*)
Nischala (Lack of exercise)
Snigdha Ahara followed by immediate exercise.
Besides these intakes of *Kanda*, *mula* and *sakha* and excessive exertion are etiological factors opined by Harita.[6] In *Anjana Nidana*, the factors which vitiates *vata*, *pitta* and *kapha* are considered under Nidana.[7] These all above *Nidana* can be included less than two heading-
1). Unwholesome diet
2). Erroneous habits.

Unwholesome diet means "which aggravates the body humours but not expel them out of the body".[8] *Charaka* has mentioned 18 types of unwholesome diet (*Viruddha Ahara*).[9]

Erroneous habits (*Viruddha chesta*) mainly included alternate use of cold and heat, suppression of natural urges, sleeping during daytime, walking at night, over indulgence in work.

Exact aetiology is unknown. Although recent work has focused on the possible role of super antigens produced by a number of microorganism including staphylococci, streptococci and mycoplasma arthritidis, other possible aetiology mechanism in RA include a breakdown in normal self tolerance leading to reactivity to self antigens in the joint such as type-II collagen or loss of immuno regulatory control mechanism resulting in polyclonal T cell activation. Superantigens are protein with the capacity to bind to HLA-DR molecules and particular V, segments of the heterodimetric T cell receptor and stimulate specific T cell expressive the V, gene products.

Of all the potential environmental triggers, the one only clearly associated with the development of RA is cigarette smoking. Rheumatism arthritis effect females in three times more than males it generally occurs in late third or fourth decade of their life spans.

Pathogenesis or *samprapti* of amavata[10]
The impairment of Agni will produce the condition of *Ama*. Mainly *agnimandya* initially affects digestion followed by metabolism. Hence in this state of Agni, the *Rasadhatu* is not formed up to the standard level & it is considered as *Ama*. This 'Ama' along with Vyana *Vayu* and also by virtue of its *Vishakari guna* it quickly moves to all *kapha sthanas*, through *Hridaya* and *Dhamanes*. This *Vidhagada Ama*, in *kapha sthana* is further contaminated by *doshas* and assumes different colours, because of the *Atipichhilata*.

If *Ama* gets obstructed in to channels and promotes further vitiation of *vata dosha*, this morbid *Ama* circulates ubiquitously in the body propelled by vitiated *vata* with predilection for *sleshma sthana*. On the *dhamanies* with the other *doshas* it facilitates *sroto abhisyanda* and *srotorodha* causing *sthanasmsraya* manifested *stabdhata* (stiffness), *sandhisula* (joint-pain), *sandhishotha* (swelling), *Anga-marda*(bodyache), *Apaka*(indigestion), *Jwara* (fever), Anga *gourava* (heaviness of body), *Alasya*(laoghess) etc symptoms of *Amavata*. According to the commentators on *Madhava Nidana* the *Samprapti* of *Amavata* can be summarized according to *Shatkriyakal*.

Pharmacodynamics
There is currently no cure for RA, the treatment strategy aims to expedite diagnosis and rapidly achieve a low disease activity state (LDAS). There are many composite scales measuring the disease activity such as the Disease Activity Score using 28 joints (DAS-28), Simplified Disease Activity Assessment Index (SDAI), and Clinical Disease Assessment Index (CDAI). To achieve full suppression of the activity of the disease (clinical remission), rheumatologists need to monitor disease activity continuously and accurately and to adjust the treatment regimen accordingly. Universally applied pharmacologic therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids have proven effective in relieving stiffness and pain, but do not moderate disease progression. Over the last 20 years, the effectiveness of DMARDs has gained much attention as these can efficiently attenuate disease activity and substantially decrease and/or delay joint deformity.[11] The therapy classification includes the traditional synthetic drugs, biological DMARDs, and novel potential small molecules. Historical DMARDs such as auranofin, minocycline, azathioprine, and cyclosporine are rarely implemented as modern therapies. Several biological DMARDs have recently emerged including TNF-inhibitor (Amjevita, Renflexis, Erelzi, Cyltezo, Imradl), anti-CD20 antibody (Truxima, Rixathon), IL-6 receptor antibody (Kevzara), RANKL antibody (Pralia), and JAK inhibitor (Olumiant). Despite the increasing number of new drugs and treatment regimes, complete long-term disease remission is not achieved for many patients and thus new therapeutic options are required.

The Ayurvedic oil no doubt about its safety and have its effect of local application, massaging due to presence of methyl salicylate, Pluchicin, zinziberine, sisamine, menthol etc. Often they are used in addition to oral NSAIDS medication. Systemic absorption from the topical oil preparation is slow taking ~10 times longer time to attain peak concentration cmpared to oral dosing. Highest blood level remains below 12% of to same dose given orally. Local concentrations are high upto a depth of 3-5 mm, i.e. in dermis, but 20 mm depth in muscles.

DISCUSSION

Pathogenesis
There are two major subtypes of RA according to the presence or absence of anti-citrullinated protein antibodies (ACPAs). Citrullination is catalyzed by the calcium-dependent enzyme peptidyl-arginine-deiminase (PAD), changing a positively charged arginine to a polar

but neutral citrulline as the result of a post-translational modification. ACPAs can be detected in approximately 67% of RA patients and serve as a useful diagnostic reference for patients with early, undifferentiated arthritis and provide an indication of likely disease progression through to RA.[12-13] The ACPA-positive subset of RA has a more aggressive clinical phenotype compared to ACPA-negative subset of RA.[14] It is reported that ACPA-negative RA has different genetic association patterns[15] and differential responses of immune cells to citrullinated antigens[12] from those of ACPA-positive subset. In terms of treatment,[16–17] less effective treatment response of methotrexate (MTX) or rituximab was observed in ACPA-negative subset. This suggests a requirement for future study on potential pathophysiology difference between these two subsets. For the purpose of this review, we will focus on the ACPA-positive subset of RA and divide the progression of RA process into several distinct stages. It is noteworthy to mention, however, that these stages may occur sequentially or simultaneously.

Triggering stage

The appearance of ACPA is now widely used to diagnose and predict RA due to its high specificity (>97%) in clinical practice. ACPA occurs as a result of an abnormal antibody response to a range of citrullinated proteins, including fibrin, vimentin, fibronectin, Epstein-Barr Nuclear Antigen 1 (EBNA-1), α-enolase, type II collagen, and histones, all of which are distributed throughout the whole body. ACPA production has been associated with genetic and environmental factors. The strongest genetic risk factor associated with ACPA-positive RA is found in genes encoding HLA-DR, especially HLA-DR1 and HLA-DR4, also known as "shared epitopes" (SEs).[18] It is thought that SE influences RA outcome via the production of ACPA and thus represents a primary risk factor for ACPA production.[19] The protein tyrosine phosphatase non-receptor type 22 (PTPN22), which is a lymphoid specific protein tyrosine phosphatase, has also drawn much attention because of polymorphisms associated with ACPA-positive RA with the contribution of PTPN22 to ACPA-positive RA among various ethnicities.[20–21] It may therefore act as a potent inhibitor of T cell activation and in turn affect in the ACPA production. Genetic variation of α1-antitrypsin has been found to be related to ACPA production in RA.[22] However, whether the production is directly linked to α1-antitrypsin deficiency per se or results from altered autophagy induced by the mutant α1-antitrypsin Z requires further study. The increased response of type I interferon gene associated with Th2 cell induction and B cell proliferation correlates with ACPA production.[23] Some researchers have recently compared the gene expression profiles between ACPA-positive RA and ACPA-negative RA patients.[24] The critical solution to the puzzle is the association between the discovered genes and ACPA production. In addition, the risks of RA increase in individuals with a family history of RA. The risk of developing RA was three times higher in first-degree relatives of RA patients even though familial factors influence RA in men and women equally.[25–26] It is also reflected in a twin study presenting recurrence risks at 9.5–13.1 in monozygotic co-twins and at 6.4–11.7 in dizygotic same sexed co-twins as opposed to a background population risk at only 0.37%.[27] Another study of 12,590 twins reveals that environment, lifestyle, and stochastic factors may also play more important roles than genetics in ACPA production while genetic factors are more responsible for the progression from ACPA-positive individuals to arthritis.[28]

The environment acts as a triggering factor for ACPA production in RA and the epigenetic regulation combines environment with genes. Gene–environment interaction influences the reactivity of autoantibodies to citrullinated antigens in RA.[29] ACPAs can be detected long before the onset of the joint symptoms. This phenomenon suggests that the joints may not be the triggering spot for autoimmunity. Lung exposure to noxious agents, including smoke, silica dust, nanosized silica, or carbon-derived nanomaterials can trigger mucosal toll-like receptors (TLRs) that activate Ca^{2+}-mediated PADs, but also antigen-presenting cells (APCs), such as classical dendritic cells (DCs) and B cells.[30–32] The coatomer subunit α gene mutations could disrupt the endoplasmic reticulum (ER)–Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis, thereby providing a connection between the lung and the joint diseases.[33] Moreover, smoking in the context of the HLA-DR SE gene may trigger RA-specific immune reactions to citrullinated proteins.[34] DNA methylation mediates smoking and genotype interaction in ANPA-positive RA.[35] There is ample evidence for three infectious agents regarded as autoimmunity triggers in RA, namely Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans (Aa), and Epstein-Barr virus (EBV). The periodontal space can also be a triggering site. In a clinic setting, 47% of the patients with RA showed evidence of previous Aa infection compared with 11% in the control group. The pathogen Aa can secret leukotoxin A and form pores in the neutrophil membranes that lead to neutrophil hyper citrullination, which results in the release of citrullinated autoantigens in the gums.[36] P. gingivalis infection leads to citrullinated autoantigens and the ACPA production in two reported ways: one way is about PAD and arginine ginpains (Rgps) of P. gingivalis, which can cleave proteins at arginine residues and citrullinate proteins producing more neoantigens;[37] another is about neutrophil extracellular trap (NET) formation induced by the P. gingivalis during the process of NETosis. ACPAs induce NETosis and in turn NETosis provides citrullinated autoantigens.[38] EBV can affect ACPA-producing B cells and impaired EBV control can be observed in RA.[39] The intestinal tract is another mucosal organ implicated in the pathogenesis of RA because dysbiosis in RA patients can result from the abundance of certain rare bacterial lineages. It is well

documented that gut microbiota may contribute to the pathogenesis of RA via multiple molecular mechanisms.[40-41] Several studies have established the role of dietary factors in RA. The omega-3 fatty acids might not only lower the risk of ACPA production but also prevent the onset of arthritis after detecting ACPAs.[42] A healthier diet can also make a contribution to reducing the risk of ACPA-positive RA occurring at 55 years of age or younger.[43] In addition, hormonal levels have been implicated in the pathology of RA[44-45] but the association with ACPA has not been firmly established. Alterations in gene expression regulation through both microRNAs and long non-coding RNAs have been proposed to contribute to the pathogenesis of RA. The contribution of other epigenetic modifications (e.g., sumoylation, histone methylation, histone acetylation, and de-acetylation) and their functional role in RA currently remain unclear. Translation of above observations to effective treatment and exploring their interaction with the genome is challenging but would be meaningful. It is of significance to clarify the detailed knowledge of each risk factor in the triggering of RA so that tools can be developed to provide susceptibility scores and early diagnosis, as well as to identify new molecular targets for personalized medicine.

Maturation Stage

This stage is initiated at the site of secondary lymphoid tissues or bone marrow. Epitope spreading refers to the development of immune responses to endogenous epitopes resulting from the release of self-antigens. The immune response to autoantigens may exist many years before disease onset and lay outside the joints. In this stage, epitope spreading and a gradually increased titer of ACPA can last several years before the onset of joint symptoms.[46] Initial ACCP levels appear to be of great importance in predicting the interval time to disease onset.[9] The production of ACPA reflects break of immunological tolerance. As a result, many citrullination neoantigens would activate MHC class II-dependent T cells that in turn would help B cells produce more ACPA. ACPA can induce pain, bone loss, and inflammation in RA.[47-48] One study has identified that two RA-specific autoantigens N-acetylglucosamine-6-sulfatase (GNS) and filamin A (FLNA) correlate microbial immunity with autoimmune responses in the joint.[49] What is more, it has been proposed that citrullination plays a unique role during osteoclast differentiation and ACPA-induced osteoclast activation which might explain important features of the gradual development of RA including why the joints are targeted. Other likely factors include biologic features of the targeted autoantigen, local microvascular, neurologic, and biomechanical factors, and microtrauma-related mechanisms may further contribute.[50]

Targeting Stage

The involvement of RA in joints usually has a characteristic presentation with synovitis occurring in symmetrical small joints. Joint swelling is the external reflection of synovial membrane inflammation following immune activation. The normal synovial compartment is infiltrated by leukocytes and the synovial fluid is inundated with pro-inflammatory mediators that interact to produce an inflammatory cascade, which is characterized by the interactions of fibroblast-like synoviocytes (FLSs) with the cells of the innate immune system, including monocytes, macrophages, mast cells, DCs, and so on, as well as cells of adaptive immune system such as T lymphocytes (cell-mediated immunity) and B cells (humoral immunity). The two immune systems and their interactions are intimately involved in the development of ACPA-positive RA, which results in the failed resolution of inflammation (chronic synovitis). Monocytes/macrophages have been found to massively infiltrate synovial membranes[51] and be central to the pathophysiology of inflammation. ACPA can enhance NF-kB activity and TNF-α production in monocyte/macrophages via binding to surface-expressed citrullinated Grp78.[52] α-Enolase on the surfaces of monocytes and macrophages induces production of pro-inflammatory mediators.[53] The imbalances between pro-inflammatory M1 macrophage and anti-inflammatory M2 macrophage must also be considered in the context of inflammatory RA.[54] Indeed, a recent study reported that an imbalance in M1/M2 monocytes contributes to osteoclastogenesis in RA patients, especially in ACPA-positive RA.[55] Further, the pro-inflammatory cytokine interleukin (IL)-17A in RA joint samples is localized primarily to mast cells based on one study[56] and mast cells can be activated by ACPA and TLRs ligand.[57] The accumulation of DCs in the articular cavity has also been reported.[58] As an APC, especially myeloid DCs have been shown to induce T cell differentiation. A detailed understanding of how myeloid DCs function in RA may provide more effective RA treatment strategies. Other possible innate immune pathways comprise neutrophil NETosis, nature killer cell activation, etc. On the other hand, many researchers place the adaptive immune system at the center of RA disease pathogenesis. Most interest in the contribution of T cells has focused on their antigen-driven role and cytokine release of specific T cell subsets. CD4 effector T cells are major drivers of abnormal immunity in RA by sustaining chronic synovitis and supporting autoantibody production and a lack of reactive oxygen species could boost pro-inflammatory T cells, which shed light on the importance of energy metabolism in RA.[59] As for B cells, the research focuses on their antigen presentation, antibody formation and release, and cytokine release into the milieu. Therefore, better understanding of the mechanisms of disordered innate immunity, including immune complex-mediated complement activation, adaptive immune responses against self-antigens, and abnormal cytokine networks may open up new avenues to restore immunologic homeostasis.

Hyperplastic Synovium

Synovium is characterized by a mixture of bone marrow-derived macrophages and specialized FLSs.[60] Synovial

cells maintain the steady state of the joint by secreting hyaluronic acid and lubricin for joint lubrication and function, as well as processing waste products. In RA, the dysfunction of FLS leads to hyperplastic synovium. The abnormal proliferation of FLS results from a loss of contact inhibition that plays a critical role in RA by producing inflammatory cytokines and proteinases, such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) that perpetuate joint destruction. They create a microenvironment that allows for the survival of T cell and B cell and neutrophil accumulation.[61] Another hypothesis regarding the cause of hyperplastic synovium is likely due to the resistance to apoptosis associated with distinctive pathways. Such pathways include abnormalities of tumor protein p53 function, which contributes to synovial lining expansion and joint destruction in RA[62] over expression of heat shock protein 70 and enhanced activation of heat shock factor 1 in RA synovial tissues that foster the survival of FLS.[63] The pathogenetic mouse model synoviolin/Hrd1 triggers synovial cell outgrowth through its anti-apoptotic effects.[64] It appears that synovial hyperplasia contains the proliferation of resident slow-cycling cells, such as mesenchymal stromal/stem cells and the infiltration of bone marrow-derived cells in lethally irradiated mice after bone marrow transplantation.[65] Although animal models of RA have been useful, they do not always reliably replicate the human disease phenotype, even less the ACPA-positive RA.

Cartilage Damage

Cartilage acts as a key component of synovial joints, consisting of chondrocytes and a dense and highly organized extracellular matrix (ECM) synthesized by these chondrocytes and contains type II collagen and glycosaminoglycans (GAGs). The hyperplastic synovium causes major damage to the cartilage in RA through directed adhesion and invasion. Conversely, inflammatory signals, including those released from the ECM, can further stimulate FLS activity. The mediators of cartilage damage include MMPs, a disintegrin-like metalloprotease with thrombospondin type 1 motifs 4 and 5 and cathepsins. MMPs are synthesized by FLS and can promote disassembly of the type II collagen network causing biomechanical dysfunction. Membrane-type I MMP is envisaged to be the predominant proteinase that degrades the collagenous cartilage matrix.[66] However, articular cartilage does not have enough regenerative potential by itself. Consequently, under the influence of synovial cytokines, particularly IL-1 and 17A, and reactive nitrogen intermediates, the cartilage is progressively deprived of chondrocytes that undergo apoptosis.[50] This results in cartilage degradation demonstrable as joint-space narrowing on radiography. These observations may help explain why RA is a site-specific manifestation of a systemic autoimmune disease, in which early cartilage damage in the context of altered immune activation leads to a specific cellular activation of FLS within the articular joints.[67] Nevertheless, a better understanding of the mechanisms underlying cartilage damage is required.

Bone Erosion

Bone loss is a pathological hallmark of RA and manifests as localized, periarticular and systemic bone loss. Bone loss is the result of the induction of osteoclasts and the suppression of osteoblasts. “Periarticular” bone loss most likely refers to cellular changes of the subchondral bone marrow, such as osteoclast differentiation and the formation of inflammatory infiltrates. It remains controversial whether inflammation or autoimmunity is the key driver for bone damage. Evidence for the traditional inflammatory theory is as follows: tumor necrosis factor alpha (TNF-α), IL-6, IL-1β, IL-17, and other inflammatory cytokines involved in RA could exert pro-osteoclastogenic effects and suppress bone formation in the appropriate environment via adequate signals, such as the receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF).[68] These promote the influx and differentiation of the monocytes into osteoclasts in the context of inflammation,[69] while anti-inflammation therapies for RA arrest the progression of bone damage and vice versa.

The second possible pathway for bone loss in RA involves two mechanisms for autoimmunity that act as a trigger for structural bone damage. The first mechanism pertains to the formation of immune complex and Fc-receptor-mediated osteoclast differentiation. The second is the formation of anti-citrullinated vimentin antibodies against the most citrullinated protein, making osteoclasts the ideal antigenic targets for anti-citrullinated protein antibodies (ACPA). It is reported that ACPA binding to osteoclast precursors induces osteoclastogenesis, bone resorption, and bone loss.[70] Bone resorption virtually creates a hole, which is usually found at spots where the synovial membrane inserts into the periosteum, which is known as a bare area according to certain anatomical features. Subchondral bone plays a vital role in maintaining the homeostasis of weight-bearing joints, and the destruction of the subchondral bone can eventually result in the degeneration of the articular cartilage. In the early stages of RA, bone marrow edema is a common finding at the spot of subchondral bone in humans and aberrant transforming growth factor-β (TGF-β) in the subchondral bone is involved at the onset of RA joint destruction in animal models.[71]

Systemic consequences

Multiple studies have documented an elevated risk of cardiovascular events in RA patients. The mechanisms responsible for this risk may be related to cytokines that increase endothelial activation and potentially make atheromatous plaques unstable. Patients with active untreated RA have reduced total cholesterol, low-density and high-density cholesterol.[72] RA also influences the brain by causing fatigue and reduced cognitive function; the lungs by causing inflammatory and fibrotic disease;

the exocrine glands by causing secondary Sjogren's syndrome; the skeletal muscles by causing sarcopenia; and the bones by causing osteoporosis. Finally, RA patients may be at greater risk of cancer, especially hematologic and kidney cancers.[73]

Research Material and Methodology should be as follow

Criteria for the Selection

A. Inclusion Criteria

Patients having signs and symptoms of Rheumatoid Arthritis with positive RA factor.

Positive Radiographic evidence of Rheumatoid Arthritis; Typical Radiographic changes of arthritis on PA view of hand & wrist radiograph that must include erosions or unequivocal bony decalcification adjacent to involve joints.

According 1987, revised criteria of American College of Rheumatology; As outlined by Sokka and Pincus studies and 2010 ACR / EULAR Rheumatoid Arthritis classification criteria for a diagnosis of Rheumatoid Arthritis

Two major anti-TNF clinical studies, ERA and ATTRACT along with other test mentioned. Patients who have failed anti-TNF therapy (inadequate responders – ir). Note; this includes patients who have failed anti-TNF therapy because of reactions.

Morning stiffness: Stiffness in and around joints lasting one hour before maximal improvement (More than 6 week's duration)

Arthritis of three or more joints (at lest three joint area, observed by Physician simultaneously having pain with soft tissue swelling or joint effusion, not just bony over growth) (More than 6 weeks duration) and Arthritis of Hand joints (More than 6 weeks duration).

Symmetric arthritis (More than 6 week's duration) and Presence of Rheumatoid Nodules Serum Rheumatoid factor- positive.

B. Exclusion Criteria

Pregnant or lactating women.

Intra articular or parenteral corticosteroids ≤ 4 weeks prior to biopsy visit (Visit 2).

Oral prednisolone more than 10mg per day or equivalent ≤ 4 weeks prior to biopsy visit (Visit 2)

Patients having systemic diseases like hypertension, renal failure, diabetes mellitus, urinary calculi, osteoporosis, osteomyelitis etc.

Patients who develop secondary complication of RA eg. Pleuro-pericardial disease. severely damaged out with bed ridden patients.

Any other serious illness eg Hepatic renal failure etc.

Patient with diagnosed other than like Gouty arthritis tuberculosis arthantis etc.

Active infection.

Septic arthritis within a native joint within the last 12 months.

Sepsis of a prosthetic joint within 12 months or indefinitely if the joint remains in situ.

Known HIV or active hepatitis B/C infection. Hepatitis B screening test must be performed at or in the preceding 3 months of screening visit.

Latent TB infection unless they have completed adequate antibiotic prophylaxis.

Malignancy (other than basal cell carcinoma) within the last 10 years

New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure.

Demyelinating disease.

Latex allergy or allergy to any excipients of Rituximab or Tocilizumab

Any other contra-indication to the study medications as detailed in their summaries of product characteristics (SmPC), including low IgG levels at clinician's discretion.

Receipt of live vaccine <4 weeks prior to first infusion

Major surgery in 3 months prior to first infusion

Presence of a transplanted organ (with the exception of a corneal transplant >3 months prior to screening)

Known recent substance abuse (drug or alcohol)

Poor tolerability of venepuncture or lack of adequate venous access for required blood sampling during the study period.

Patients unable to tolerate synovial biopsy or in whom this is contraindicated including patients on anti-coagulants (oral anti-platelet agents are permitted)

Patients currently recruited to other clinical trial(s) involving an investigational medicinal product (except any observational follow-up periods not involving an IMP).

Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that would impart, in the judgment of the investigator, excess risk associated with study participation or study drug administration, or which, in the judgment of the investigator, would make the patient inappropriate for entry into this study.[74]

Variables

1. Independent Variable

Pain, swelling with stiffness.

Joint degeneration (radiographs).

Range of Joint motion.

Gender.

Age range.

Others

2. Dependent variable

Pain (Visual Analogue scale & Oxford pain chart).

Self-reported disability (Questionnaire).

Observed disability (Performance of tasks).

Others

Tools of the study

Criteria of Assessment

A. Subjective Parameter (Sign & Symptoms)-

1. Shoola(Pain)
2. Shotha(Swelling)
3. Graha(Stiffness)
4. Sandhi Atopa(Crepitus)

5. Aushnyata(Temprature)
6. Guruta(Heaviness)

B. Objective Parameter-
Oxford Pain Chart
WOMAC index score and Visual Analog Scale
WHO- QOL score
Others

Assessment tools used in Methodology
1. WOMAC- **VAS** (Modified –CRD**:** Centre for Rheumatic Disease, Pune version)
2. Quality of Life Index-WHO QOL BREF Score:
3. Oxford Pain Chart.
4. Others

Criteria for routine examination and assessment
The full details of history and physical examination of the patient were recorded in proforma. The assessment should be done according to the effect of the drugs on each of the cardinal manifestations of the disease, general functional ability of the patient and the pathological/bio-chemical changes. A score system has been evolved as mentioned for gradation of the severity of the disease.

Pain
Grade 0 - No pain - score-0
Grade 1 - Mild pain - score-10
Grade 2 - Mild pain at rest, severe on movement - score-20
Grade 3 - Moderate pain at rest/ severe on movement - score-30

Stiffness of joint
Grade 0 - Stiffness of joint less than 5 minutes - score-0
Grade 1 - Stiffness of joint 5 minutes to 1 hour - score-10
Grade 2 - **S**tiffness of joint 2 to 8 hours - score-20
Grade 3 - **S**tiffness of joint more than 8 hours - score-30

Onset of fatigue
Grade 0 - Not feeling of tiredness after 12 hours activity - score-0
Grade 1 - Feels tired after 8 hours activity - score-10
Grade 2 - Feels tired after 5 hours activity - score-20
Grade 3 - Feels tired after 1/2 hour activity - score-30

Swelling of joint
Grade 0 - No swelling at all - score-0
Grade 1 - Swelling noticeable but not masking the bony prominence - score-5
Grade 2 - Swelling sufficient to cover the bony prominence - score-10
Grade 3 - **S**welling with covering the bony prominences with fluctuation - score-15

Range of Movement
Grade 0 - No restriction of movement - score-0
Grade 1 - 10% or less restriction of movement - score-4
Grade 2 - 20% or less restriction of movement - score-8
Grade 3 - 30% or less restriction of movement - score-16

General function/Functional class
Grade 0 - Carry out normal physical activities with out any discomfort - score-0
Grade 1 - Carry out normal physical activities with some discomfort - score-3
Grade 2 - Carry out normal physical activities with some discomfort -score-6
Grade 3 - Incapacitated and bedridden unable self care - score-9

Grip strength
Grade 0 - Can **r**aise the mercury column above 250 mm. of Hg. by pressing the cuff - score- 0
Grade 1 - Can raise the mercury column less than 200 mm. of Hg. by pressing the Cuff - score-10
Grade 2- Can raise the mercury column less than 100 mm. of Hg. by pressing the cuff - score -20
Grade 3 - Can raise the mercury column less than 20 mm. of Hg. by pressing the cuff - score-30

Joint Count
Grade 0 - If the joint count recorded as per above is less than 5 - score-0
Grade 1 - If the joint count recorded, is up to 50 - score-10
Grade 2 - If the joint count noted, is up to 100 - score-20
Grade 3 - It the joint count is above 150 - score-30

Elevated ESR/presence of subcutaneous nodules/ deformity/low grade fever
Grade 0 - ESR within normal limits no subcutaneous nodules, deformity of joints and low grade fever - score-0.
Grade 1 - Presence of any one of the four i.e. raised ESR subcutaneous nodules, deformed joints, or low grade fever - score-3
Grade 2 - If any of the two is present - score-6
Grade 3 - If all of the four are present - score-9

Table 1: General Observations.

Sl. No.	Observations	Percentage
1.	Age group (In years)	….
2.	Gender	….
3.	Religion	….
4.	Educated	….
5.	Illiterate/ Field Worker with labor	….
6.	Vegetarian	….

7.	Chronicity (6-12 months)	….
8.	Morning stiffness	….
9.	Joint Pain	….
10.	Swelling	….
11.	Restriction of joint	….
12.	Fever	….
13.	Constipation	….
14.	Loss of appetite	….
15.	Anorexia	….

Future Perspective

With a better understanding of the patho- physiology of RA, new therapeutic approaches are emerging to provide precise medicine for individuals. However, the function and adverse side effects of these drugs will need to be carefully evaluated and used reasonably. Gene therapy means that treating RA by inserting a gene into a patient's cells instead of using drugs. Targeting gene therapy in RA is a treatment strategy that is still in very early stages of development but could lead to new possibilities because of treating a disease at its root. The availability of Notch1 targeting siRNA delivery nanoparticles and TNF-α gene silencing using polymerized siRNA/Thiolated Glycol Chitosan Nanoparticles has been tested relatively successfully in an animal model. To prevent disease onset or relapses, smoking cessation or avoiding body exposure to environment risk factors is probably the easiest and most cost-effective method. Autoimmunity (tolerance break) develops years before the inflammatory phase of the disease, which can be considered as a golden period for preventing disease progression. Reestablishing immune tolerance and immunological homeostasis are ambitious goals in the way to overcome the disease. T cells and B cells can be targeted by specific drugs in the future to achieve sero- conversion or delay the onset of joint destruction. Reduction of the function of APCs and modification of the pro-inflammatory properties of antibodies are being further developed. There is also a great interest in the novel approaches that have the possibility of becoming vital therapeutic targets, such as TLRs; Bruton's tyrosine kinase; phosphoinositide-3-kinase pathway; TGF-β; neuro pathways, and DCs. Bruton's tyrosine kinase is involved in various signaling pathways downstream of the pre-B-cell receptor and FcR, which is a promising therapeutic target for RA. Thus, the safety and tolerability of the medicines/ intravenous infusions of expanded adipose-derived stem cells in refractory RA will be reported or easily assessed. In fact, new pathologic insight will support new avenues for therapeutic development.

CONCLUSION

Researchers would understand the Ayurvedic, modern and pathological diagnostic procedure for the above mentioned disease, in addition to careful history taking and examination. Beyond the above the scholar also will learn about the various aspects of pathological researches and medications affect pathway. This will develop a new scenario in Ayurveda with efficient medication and researches in modern era.

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