

Historical and Contemporary Perspectives on Rheumatoid Arthritis: A Multifaceted Approach

Nadia Rashid Al-Hassan, Ahmed Adel Abdulla

Nadia Rashid Al-Hassan, Department of Biological Sciences, Faculty of Science, University of Basrah, Iraq; Ahmed Adel Abdulla, Institute of Biomedical Research, College of Medicine and Health Sciences, University of Duhok, Iraq

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ABSTRACT

The pharmacological mechanisms of the medicinal plants traditionally used for RA in Persian medicine are discussed in the current review. Further investigations are mandatory to focus on bioefficacy of these phytochemicals for finding novel natural drugs. Rheumatoid arthritis is chronic, progressive, disabling autoimmune disease characterized by systemic inflammation of joints, damaging cartilage and bone around the joints. It is a systemic disease which means that it can affect the whole body and internal organs such as lungs, heart and eyes. Although numbers of synthetic drugs are being used as standard treatment for rheumatoid arthritis but they have adverse effect that can compromise the therapeutic treatment. Unfortunately, there is still no effective known medicinal treatment that cures rheumatoid arthritis as the modern medicine can only treat the symptoms of this disease that means to relieve pain and inflammation of joints. It is possible to use the herbs and plants in various forms in order to relieve the pain and inflammation in the joints. There are so many medicinal plants that have shown anti rheumatoid arthritis properties. So the plants and plant product with significant advantages are used for the treatment of rheumatoid arthritis. The present review is focused on the medicinal plants having anti rheumatoid arthritis activity.

Keyword: Arthritis, Stages, Epidemiology, Pathogenesis, Diagnosis, Treatment.

INTRODUCTION

Rheumatoid arthritis

RA can cause economic burden, where it can severely restrict a person's ability to carry out tasks related to work and may even force an individual to reduce the amount they work or make changes in employment to accommodate their disability. In some cases, where the disease is severe, a person may be forced to leave the workforce altogether. All of these scenarios translate to lost income over the course of a lifetime¹. One study found that restrictions in work often affect individuals with RA early in the course of the disease, with the use of disability benefits increasing sharply within 2 years of diagnosis². Another study that looked at the economic burden imposed by RA and osteoarthritis found that patients with RA had significantly higher expenses in terms of home care, child care, use of medical equipment and devices, and home remodeling than people without the disease. Patients with RA also had a significantly higher economic burden than patients with osteoarthritis and were 3 times more likely to have had a reduction in household income. Compared with osteoarthritis patients, individuals with RA had a greater reduction in work hours and a greater likelihood of having lost a job or taken early retirement. Additionally, a significantly higher percentage of RA patients in the study were unable to find work because of their condition compared with both osteoarthritis patients and people without either disease³.

History

As many chronic diseases, the history of rheumatoid arthritis started around 1500 BC when Ebers Papyrurales

describe a condition similar to rheumatoid arthritis. Several reports suggest that mummies from different eras have deformities that are pathognomonic of arthritis, however, was not until later 1800 where this chronic condition was named by Garrod rheumatoid arthritis, replacing the terms arthritis deformans and rheumatic gout⁴⁻⁶. Thomas Sydenham and later on, Beauvais pointed out that RA has a chronic progressive course especially in the tendon sheaths and bursa causing damage of the bone and cartilage⁵.

Definition of Rheumatoid arthritis

Rheumatoid arthritis is derived from the Greek word $\rho\acute{\epsilon}\upsilon\mu\alpha$ -rheuma (nom.), $\rho\acute{\epsilon}\upsilon\mu\alpha\tau\omicron\varsigma$ -rheumatos (gen.) ("flow, current"). The suffix -oid ("resembling") gives the translation as joint inflammation that resembles rheumatic fever. Rhuma which means watery discharge might refer to the fact that the joints are swollen or that the disease may be made worse by wet weather⁷. Rheumatoid arthritis (RA) is a long-lasting autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body. The disease may also affect other parts of the body. This may

result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart. Fever and low energy may also be present. Often, symptoms come on gradually over weeks to months². Rheumatoid arthritis is an inflammatory rheumatic disease with progressive course

affecting articular and extra-articular structures resulting in pain, disability and mortality. RA causes premature death, disability, and lowers the quality of life in the industrialized and developing world⁸. Persistent inflammation leads to erosive joint damage and functional impairment in the vast majority of patients^{9,10}. The onset of disease is not similar in all patients but varies in regard to type, number, and the pattern of joint involvement. The course of disease may be also different according to the presence or absence of several variables including genetic background, frequency of swollen joints, autoantibody in the serum and the severity of inflammatory process^{11,12}. RA causes are unknown, but it is believed to result from a faulty immune response. RA can begin at any age and causes fatigue and prolonged stiffness after rest. There is no cure for RA, but effective drugs are increasingly available to treat RA and prevent deformed joints. In addition to medications and surgery, scientifically-proven self-management (techniques that people use to manage their condition on a daily basis and pursue the activities important to them) approaches, such as exercise, can reduce pain and disability.

Stages of RA

Early detection and treatment to control inflammation is of critical importance in RA, given the potential for rapid destruction of joint and other tissue and impairment of functioning. Although how RA progresses in individual patients and the pattern of joint involvement varies widely from patient to patient, in the majority of patients with RA (70%) some degree of joint erosion in the hands and feet is detectable by x-ray within the first two years of the disease¹³. Without adequate treatment, at 20 years after diagnosis, more than 60% of patients with RA may develop significant functional impairment (stage III), including need of mobility aids, loss of ability for self-caring, and requirement of joint replacement, or experience loss of independence and require daily care (stage IV)¹³.

Stage I.

Early stage RA (stage I) is characterized by synovitis, or an inflammation of the synovial membrane, causing swelling of involved joints and pain upon motion. During this stage, there is a high cell count in synovial fluid as immune cells migrate to the site of inflammation. However, there is generally no x-ray evidence of joint destruction, with the exception of swelling of soft tissues and possibly evidence of some bone erosion¹⁴.

Stage II.

In moderate RA, stage II, there is a spread of inflammation in synovial tissue, affecting joint cavity space across joint cartilage. This inflammation will gradually result in a destruction of cartilage, accompanied by a narrowing of the joint¹⁴.

Stage III.

Severe RA, stage III, is marked by formation of pannus in the synovium. Loss of joint cartilage exposes bone beneath the cartilage. These changes will become evident on x-ray, along with erosions around the margins of the joint. Joint deformities may also become evident¹⁴.

Stage IV.

Stage IV is called terminal or end stage RA. The inflammatory process has subsided and formation of fibrous tissue and/or fusing of bone results in ceased joint function. This stage may be associated with formation of subcutaneous nodules¹⁴. These stages are more clarified in *Figure 1*.

Classification criteria and clinical manifestations

The new criteria proposed by the ACR/EULAR in 2010 allows to classify RA on earlier stages, that permit to prevent bone destruction and radiological progression thanks to the use of disease-modifying drugs^{15,16}. Gradual onset polyarthralgia with symmetrical, intermittent and migratory joint involvement, especially in the hands and feet are most typical clinical presentations of RA. Symmetrical inflammation of small and large articulations accompanied by morning stiffness it's a common symptoms of RA. At the same time, modern classification criteria contribute in changes of the clinical picture of the disease, increasing amount of seronegative mono- and oligoarthritis as early clinical manifestation and increase risk of false positive diagnostics among patients with autolimiting undifferentiated arthritis¹⁷. The new criterion is not a diagnostic criterion but a classification criterion to identify disease with a high likelihood of developing a chronic form. However, a score of 6 or greater unequivocally classifies a person with a diagnosis of rheumatoid arthritis¹⁶. The "new" classification criteria, jointly published by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) establish a point value between 0 and 10. Four areas are covered in the diagnosis¹⁶.

Epidemiology

RA affects approximately 0.5 to 1% of the population worldwide, with women 2 to 3 times as likely as men to develop the disease¹⁸. Its annual incidence in Finland is estimated at 44.5 per 100 000 (58.6 for women, 29.5 for men)¹⁹. Studies in industrialized countries show annual incidences between 5 and 50 per 100 000, with results varying based on case identification methods and geographical differences. RA is especially common in northern Europe and North America. Age at onset is usually between 30 and 70, but at no age is one immune. Evidence suggests that RA incidence may be declining, with disease onset shifting towards older age groups^{20,21}.

Pathogenesis

RA is characterized not only by local inflammation damaging small and medium-sized joints but also by systemic inflammation. Different autoimmune and inflammatory processes are variably active in RA, making the entire disease entity clinically and pathobiologically heterogeneous. The common denominators of differing RA subsets, such as autoimmunity and inflammation, are of key interest²².

Synovial Immunologic Processes and Inflammation

Synovitis occurs when leukocytes infiltrate the synovial compartment. Leukocyte accumulation primarily reflects migration rather than local proliferation. Cell migration is enabled by endothelial activation in synovial microvessels, which increases the expression of adhesion molecules

(including integrins, selectins, and members of the immunoglobulin superfamily) and chemokines.

Accordingly, neoangiogenesis, which is induced by local hypoxic conditions and cytokines, and insufficient lymphangiogenesis, which limits cellular egress, are characteristic features of early and established synovitis. These microenvironmental changes, combined with profound synovial architectural reorganization and local fibroblast activation, permit the buildup of synovial inflammatory tissue in rheumatoid arthritis.

Adaptive Immune Pathways

The genetics of rheumatoid arthritis and the presence of autoantibodies clearly place adaptive immunity at the center of early pathogenesis. However, even though T cells are abundant in the synovial milieu, the functional role of T cells remains insufficiently understood. Direct targeting of T cells by cyclosporine or T-cell-depleting therapeutics has shown limited or no efficacy²⁵. This finding may reflect “broad spectrum” deletion of regulatory as well as effector T cells and suggests the need to target T-cell subsets. The synovium in rheumatoid arthritis contains abundant myeloid cells and plasmacytoid dendritic cells that express cytokines (interleukin-12, 15, 18, and 23), HLA class II molecules, and costimulatory molecules that are necessary for T-cell activation and antigen presentation^{26,27}. Moreover, the use of abatacept (a fusion protein containing cytotoxic T-lymphocyte-associated antigen 4 and the FC fragment of IgG1) to disrupt antigen presentation by blocking T-cell costimulation (through the interaction of CD28 with CD80 or CD86) is efficacious in rheumatoid arthritis. Autoreactive T cells against citrullinated self-proteins have been identified. Synovial T-cell oligoclonality, germinal-center reactions, and B-cell hypermutation suggest ongoing local antigen-specific, T-cell-mediated B-cell help^{28,29}.

Activation of the Innate Immune System A variety of innate effector cells, including macrophages, mast cells, and natural killer cells, are found in the synovial membrane, whereas neutrophils reside mainly in synovial fluid. Macrophage colony-stimulating factor, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor (GM-CSF) enhance maturation of these cells, their efflux from the bone marrow, and trafficking to the synovium. In particular, macrophages are central effectors of synovitis; clinically effective biologic agents consistently reduce macrophage infiltration in the synovium³⁰. Macrophages act through release of cytokines

(e.g., TNF- α and interleukin-1, 6, 12, 15, 18, and 23), reactive oxygen intermediates, nitrogen intermediates, production of prostanoids and matrix-degrading enzymes, phagocytosis, and antigen presentation. This pattern of expression of proinflammatory cytokines and inducible nitric oxide synthase suggests a predominant M1 macrophage phenotype. Macrophages are activated by toll-like receptors (TLRs) (e.g., TLR 2/6, 3, 4, and 8) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) that recognize a range of pathogen-associated molecular patterns and damage-associated molecular patterns that potentially include bacterial, viral, and putative endogenous ligands³¹. Macrophage activation is also driven by cytokines, cognate

interactions with T cells, immune complexes, lipoprotein particles and liver X-receptor agonists (e.g., oxysterols, oxidized low-density lipoprotein [LDL], and serum amyloid A-rich high-density lipoprotein [HDL]), and the protease-rich microenvironment through protease-activated receptor 2³². Moreover, microRNA species (e.g., microRNA-155) have been implicated in the regulation of synovial cytokine expression^{33,34}. Neutrophils contribute to synovitis by synthesizing prostaglandins, proteases, and reactive oxygen intermediates³⁵. Mast cells that produce high levels of vasoactive amines, cytokines, chemokines, and proteases, through ligation of TLR, suppression of tumorigenicity 2 (ST2), Fc receptor γ , and Fc receptor ϵ , also play a role^{36,37}. A fraction of ACPA belongs to the IgE class, which may elicit mast-cell activation through Fc receptor ϵ ³⁸. These findings, which provide evidence that activation of the innate immune pathway contributes to synovitis, could lead to the development of treatments that modulate TLR-dependent, NLR-dependent, and inflammasome-dependent pathways. *Cytokines and Intracellular Signaling Pathways*

Cytokine production that arises from numerous synovial cell populations is central to the pathogenesis of rheumatoid arthritis. Cytokine patterns may shift over time; early rheumatoid arthritis has an apparently distinct cytokine profile, involving the expression of interleukin-4, 13, and 15³⁹ that subsequently evolves in chronic disease. TNF- α plays a fundamental role through activation of cytokine and chemokine expression, expression of endothelial-cell adhesion molecules, protection of synovial fibroblasts, promotion of angiogenesis, suppression of regulatory T cells, and induction of pain^{40,41}. Similarly, interleukin-6 drives local leukocyte activation and autoantibody production but mediates systemic effects that promote acute-phase responses, anemia, cognitive dysfunction, and lipid-metabolism dysregulation. The central role of these two cytokines has been confirmed by successful therapeutic blockade of membrane and soluble TNF- α and the interleukin-6 receptor in patients with rheumatoid arthritis. Interleukin-1 family cytokines (e.g., interleukin-1 α , 1 β , 18, and 33) are abundantly expressed in rheumatoid arthritis. They promote activation of leukocytes, endothelial cells, chondrocytes, and osteoclasts^{42,43}. However, clinical benefits after interleukin-1 inhibition have been modest. Although this paradox is not fully understood, it may reflect functional redundancy in the canonical TLR and interleukin-1-receptor signaling pathways. Other efforts to target cytokines (e.g., interleukin-17 and 17 receptor, BLYS, APRIL, and GM-CSF) with the use of biologic approaches are ongoing. The range of available therapeutics based on the biologic characteristics of synovial cytokines will probably expand. Elucidation of the complex intracellular signaling molecules (particularly kinases) that regulate cytokine-receptor-mediated functions may facilitate the development of specific small-molecule inhibitors. Although many intracellular signaling pathways are active in the synovium, clues to those with hierarchical importance have been provided by clinical trials.

Mesenchymal Tissue Responses

The normal synovium contains mesenchymal-derived, fibroblast-like synoviocytes (FLSs) and resident macrophages. In rheumatoid arthritis, the membrane lining is expanded, and FLSs assume a semiautonomous phenotype characterized by anchorage independence, loss of contact inhibition, and the expression of high levels of disease-relevant cytokines and chemokines, adhesion molecules, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs)⁴⁴. FLSs thereby contribute directly to local cartilage destruction and the chronicity of synovial inflammation, and they promote a permissive microenvironment that sustains T-cell and B-cell survival and adaptive immune organization⁴⁵.

The molecular mechanisms that sustain synovial hyperplasia are incompletely understood. The increased proliferative capacity of FLSs is not explanatory. A more likely possibility is altered resistance to apoptosis, which is mediated by diverse pathways, including mutations of the tumor-suppressor gene p53⁴⁶; expression of stress proteins (e.g., heat-shock protein 70), which foster the survival of FLSs⁴⁷; and modulation of the function of the endoplasmic reticulum by synoviolin, an E3 ubiquitin ligase that regulates the balance of cell proliferation and apoptosis⁴⁸. Synoviolin negatively regulates p53 expression and its biologic functions. In addition, cytokine-induced activation of the NF- κ B pathway in FLSs favors survival after ligation of TNF- α receptor. Methylation and acetylation of cell-cycle regulatory genes and expression of microRNAs may be critical factors⁴⁹. Synovial hyperplasia could also reflect increased influx of mesenchymal cells. In a mouse model of arthritis with severe combined immunodeficiency, FLSs were shown to migrate and thereby promote articular involvement⁵⁰. A crucial advance has been the elucidation of the molecular pathways that sustain integral membrane structure in rheumatoid arthritis. Cadherin-11 and β -catenin mediate FLS-homotypic interactions that are essential for membrane formation and for subsequent inflammation⁵¹.

Diagnosis

RA is diagnosed using information from physical examination (signs and symptoms). Ideally, RA is diagnosed early - within 6 months of symptom onset, so that treatment that slows or stops disease progression can begin. No test results are pathognomonic for rheumatoid arthritis (RA); instead, the diagnosis is made by using a combination of clinical, laboratory, and imaging features.

Imaging

X-rays of the hands and feet are generally performed in people with a many joints affected⁵². In RA, there may be no changes in the early stages of the disease, or the X-ray may demonstrate juxta-articular osteopenia, soft tissue swelling and loss of joint space. As the disease advances, there may be bony erosions and subluxation. X-rays of other joints may be taken if symptoms of pain or swelling occur in those joints. Other medical imaging techniques such as magnetic resonance imaging (MRI) and ultrasound are also used in diagnosing the disease⁵³. Magnetic resonance imaging (MRI) is useful in detecting RA before radiographic changes can be detected. MRI is

more sensitive in detecting erosions, and it is capable of identifying bone marrow edema and synovial hypertrophy. Both of these findings predict the development of erosive disease⁵⁴. Radiography remains the first choice for imaging in RA; it is inexpensive, readily available, and easily reproducible, and it allows easy serial comparison for assessment of disease progression^{55,56}. Views of the hands, wrists, knees, feet, elbows, shoulders, hips, cervical spine, and other joints should be assessed with radiography when indicated (see images below). Erosions may be present in the feet, even in the absence of pain and in the absence of erosions in the hands. Ultrasonography is used infrequently in establishing a diagnosis of RA, and it is more sensitive in detecting synovial and tendon inflammation than clinical examination alone^{57,58}. Ultrasonography might also be useful in guided joint aspiration and injection. Ultrasonography of joints is gaining increased widespread acceptance in clinical practice; however, its use in RA is not yet the standard of care⁵⁹⁻⁶². Ultrasonography allows recognition of effusions in joints that are not easily accessible (e.g., the hip and, in obese patients, the shoulder) and of cysts (Baker cysts). In addition, high-resolution sonograms allow visualization of tendon sheaths, changes and degree of vascularization of the synovial membrane, and even erosions.

Ultrasonography can often be done in the office. High-frequency transducers (10 MHz or higher) have improved the spatial resolution of ultrasound images; these images can depict 20% more erosions than conventional radiography. Also, color Doppler and power Doppler ultrasound, which show vascular signals of active synovitis depending on the degree of inflammation, are useful in assessing synovial inflammation. This is important, since in the early stages of RA, the synovium is primarily affected, and synovitis seems to be the best predictive marker of future joint damage⁶³.

Blood tests

Routine viral screening by serologic testing does not significantly facilitate the diagnosis of RA in patients with early RA, nor is it helpful as a potential identifier of disease progression⁶⁴. Potentially useful laboratory studies in suspected RA fall into 3 categories—markers of inflammation, hematologic parameters, and immunologic parameters—and include the following:

- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP) level
- Complete blood count (CBC)
- Rheumatoid factor (RF) assay
- Antinuclear antibody (ANA) assay
- Anti-cyclic citrullinated peptide (anti-CCP) and anti-mutated citrullinated vimentin (anti-MCV) assays

(currently used in the 2010 American College of Rheumatology [ACR]/European League Against Rheumatism [EULAR] classification criteria).

- Anti filaggrin antibodies (AFA)
- Micro RNA (miRNA)

Treatment

After RA has been diagnosed and an initial evaluation performed, treatment should begin. Recent guidelines have addressed the management of RA^{65,66}, but patient preference also plays an important role. There are special considerations for women of childbearing age because many medications have deleterious effects on pregnancy. Goals of therapy include minimizing joint pain and swelling, preventing deformity (such as ulnar deviation) and radiographic damage (such as erosions), maintaining quality of life (personal and work), and controlling extraarticular manifestations⁶⁷.

Drug Therapy

There are five main drug classes that are currently used for treatment and they include analgesics, disease-modifying antirheumatic drugs (DMARDs), anticytokine therapies, glucocorticoids, and nonsteroidal anti-inflammatory drugs (NSAIDs)⁶⁷.

Analgesics

Analgesics provide pain relief from mild to moderate arthritis. Included in this class are acetaminophen, tramadol, capsaicin, and narcotics. Due to the fact these drugs do not exhibit any antiinflammatory properties, they are usually combined with NSAIDs, glucocorticoids, DMARDs, and anticytokine therapies⁶⁷.

Disease-modifying antirheumatic drugs (DMARDs)

Disease-modifying antirheumatic drugs (DMARDs) are the mainstay of RA therapy. DMARDs can be biologic or nonbiologic. Biologic agents include monoclonal antibodies and recombinant receptors to block cytokines that promote the inflammatory cascade responsible for RA symptoms. *Methotrexate (MTX)*

Methotrexate is recommended as the first-line treatment in patients with active RA, unless contraindicated or not tolerated. MTX is a folic acid antagonist, but its precise mechanism of action in RA treatment is unknown. MTX acts within weeks to diminish disease activity. It has also been shown to decrease radiographic progression of disease⁶⁸. MTX can be used in combination with other DMARDs to achieve and maintain disease remission. Although initially the potential hepatotoxicity of MTX caused concern, long-term follow-up of patients on chronic MTX therapy has alleviated many of these worries. Serious irreversible liver damage is rare in patients who do not have hepatitis and who consume minimal amounts of alcohol and have regular laboratory monitoring. Generally, liver enzymes are measured after 1 month of therapy, and are repeated at 8- to 12-week intervals after a stable dose is established⁶⁹. MTX can result in a hypersensitivity-type reaction, MTX-associated pneumonitis that can manifest with nonspecific symptoms such as fever, fatigue, cough, or dyspnea. When this diagnosis is suggested, MTX should be discontinued immediately. This manifestation can be indistinguishable from infection, and appropriate investigations and treatment for both should be initiated immediately. Biopsy may be necessary to establish the diagnosis⁶⁹. Because the half-life of MTX primarily depends on renal function, patients with chronic renal insufficiency should not be treated with this agent. To minimize alopecia, mouth ulcers, nausea, and hepatic

toxicity, folic acid (1-2 mg/day) should be given to all MTX-treated patients⁶⁹.

Hydroxychloroquine, Sulfasalazine, and Leflunomide

Leflunomide (Arava) may be used as an alternative to methotrexate, although gastrointestinal adverse effects are more common. Sulfasalazine (Azulfidine) or hydroxychloroquine (Plaquenil) is recommended as monotherapy in patients with low disease activity or without poor prognostic features (e.g., seronegative, nonerosive RA). Hydroxychloroquine and sulfasalazine are DMARDs that provide mild anti-inflammatory activity in most patients. They are both well tolerated and have few side effects. Leflunomide, a pyrimidine synthesis inhibitor, is also used as add-on therapy with MTX or other agents. Leflunomide can cause liver enzyme elevation and requires regular liver enzyme monitoring. Two important combination strategies have been tested and reported.

Triple therapy combining sulfasalazine, hydroxychloroquine, and MTX is more effective than monotherapy and not more toxic⁷⁰. The Best trial demonstrated that initial treatment with MTX combined with an anti-tumor necrosis factor (anti-TNF) agent was the safest and most effective therapy when compared with three less-aggressive strategies⁷¹.

Anti-Tumor Necrosis Factor Agents

TNF inhibitors are the first-line biologic therapy and are the most studied of these agents. If TNF inhibitors are ineffective, additional biologic therapies can be considered. Simultaneous use of more than one biologic therapy (e.g., adalimumab [Humira] with abatacept [Orencia]) is not recommended because of an unacceptable rate of adverse effects. They are most often added to MTX or other ongoing therapy. A bonus effect of the anti-TNF agents in RA is their impact on vascular function. Endothelium-dependent vasodilation, a marker of endothelial function, is improved by anti-TNF therapy, suggesting a potential protective effect on vascular function⁷². Before therapy with an anti-TNF agent is initiated, patients should be screened by skin test and chest radiograph for the presence of tuberculosis. TNF has an important role in the formation of granulomas; this was recognized when reactivation tuberculosis emerged as a complication of anti-TNF therapy. The anti-TNF agents also have other significant immunosuppressive effects. Infections in patients being treated with these agents can progress more rapidly and follow a more fulminant course. Signs and symptoms of any significant infectious process (e.g., anything requiring antibiotic, antiviral, or antifungal therapy) mandate the temporary discontinuation of any of these agents until the infection is resolved. The role of these agents in the development of hematologic malignancies is unclear. Although the development of lymphomas during therapy with these agents has been documented, as previously discussed, these occur de novo at higher rates in patients with RA. No further malignancy evaluation outside of routine health screening is advised for patients on anti-TNF therapies. The development of a malignancy, however, is an indication to discontinue anti-TNF therapy. The significance of the induction of antinuclear and other autoantibodies by anti-TNF agents is unclear because most patients with this phenomenon do not phenotypically

express autoimmune syndromes associated with these antibodies. The relation of anti-TNF therapy to congestive heart failure is unclear. Studies of anti-TNF therapy for the treatment of heart failure were discontinued because of lack of efficacy, and a few studies have associated high doses of infliximab with exacerbation of congestive heart failure in patients with preexisting cardiovascular disease^{73,74}. However, this finding is controversial. A study by Wolfe and Michaud⁷⁵ found that patients with RA, when compared with patients with OA, have an increased incidence of heart failure at baseline. However, patients with RA in this study who were treated with an anti-TNF agent had a decreased incidence of heart failure. The standard of care is avoidance of anti-TNF therapy in decompensated heart failure. A rare but potentially devastating adverse effect of anti-TNF therapies is demyelinating disease. New-onset multiple sclerosis, optic neuritis, and transverse myelitis have been reported with anti-TNF therapy⁷⁶⁻¹⁰⁹.

Glucocorticoids

Glucocorticoids (GCs) are a class of corticosteroids, which are a class of steroid hormones. Glucocorticoids are corticosteroids that bind to the glucocorticoid receptor (GR)¹¹⁰. Corticosteroids are potent anti-inflammatory drugs that are commonly used in patients with RA to bridge the time until treatment with DMARDs is effective^{111,112}. These agents are effective adjuncts to DMARD or NSAID therapy. Timely dose reductions and cessation are important because of the adverse effects associated with long-term steroid use. Corticosteroids can be administered by oral, IV, or intra-articular routes. The most commonly used glucocorticoids are prednisone or prednisolone⁶⁷. Glucocorticoids are an established therapy for inflammatory conditions, used in clinical practice for >60 years¹¹³. In RA, glucocorticoids were initially used at high doses for the short-term treatment of flares, but there is increasing interest in the use of lower dose therapy (<10 mg/day) given for prolonged periods (>6 months). The addition of long-term low-dose glucocorticoid therapy to standard disease-modifying treatments has been shown to reduce pain and improve patient quality of life, but also to reduce the development of erosions, suggesting a disease-modifying action¹¹⁴. One study found that the use of corticosteroids was associated with heart failure in patients with RA, independent of cardiovascular risk factors and coronary heart disease (CHD). Those patients who currently used MTX showed a lower risk of heart failure¹¹⁵.

Nonsteroidal anti-inflammatory drugs (NSAIDs) Drug therapy for RA may involve NSAIDs and oral, intramuscular, or intra-articular corticosteroids for controlling pain and inflammation. Ideally, NSAIDs and corticosteroids are used only for short-term management. DMARDs are the preferred therapy. NSAIDs have both analgesic and anti-inflammatory properties but do not change disease outcomes¹¹⁶. The drugs in this class include ibuprofen, aspirin, naproxen, and indomethacin. They reduce both pain and stiffness in those with RA²⁰. Generally they appear to have no effect on people's long term disease course and thus are no longer first line agents. NSAIDs should be used with caution in those with

gastrointestinal, cardiovascular, or kidney problems. Use of methotrexate together with NSAIDs is safe, if adequate monitoring is done. NSAIDs inhibit COX-1 and COX-2, which block prostaglandin synthesis. Although NSAIDs are essential to the treatment of RA, they can cause severe GI distress and ulcers. On the other hand, selective COX2 inhibitors are also just as useful in the treatment of RA, but have a lower severity of these adverse GI side effects. These drugs include celecoxib and valdecoxib and are similar to the NSAIDs except that they do not have the same corrosive effects on the GI lining. However, when administering these drugs, the patients' medical history must be assessed to ascertain that cardiovascular disease is not significant. COX-2 inhibitors are associated with reduced PGI2 production by vascular endothelium with little or no inhibition of potentially thrombotic platelet thromboxane A2 production. This, in turn, predisposes to endothelial injury, which can increase ischemic cardiovascular events²¹. COX-2 inhibitors, such as celecoxib, and NSAIDs are equally effective. They have a similar gastrointestinal risk as an NSAIDs plus a proton pump inhibitor²². In the elderly there is less gastrointestinal intolerance to celecoxib than to NSAIDs alone²³. There however is an increased risk of myocardial infarction with COX-2 inhibitors. Anti-ulcer medications are not recommended routinely but only in those high risk of gastrointestinal problems.

CONCLUSION

To conclude, numerous in vitro, preclinical and clinical studies have confirmed the beneficial effects of traditionally used medicinal plants for the management of RA pathogenesis and its complications in traditional Persian medicine. Limited human studies suggest that traditional medicinal plants used for RA have less adverse effects than conventional drugs. Results obtained from pharmacological studies indicate a necessity to establish bioefficacy, optimum dosage and duration of treatment. Further well-designed human clinical trials are required to evaluate the effects of traditional natural remedies in terms of symptomatic, functional and biological outcomes. Current natural agents may also be tested as adjunctive therapies in combination with conventional drugs for RA.

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