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Rheumatic disease: Risk factors, pathophysiology and management

Gudisa Bereda*

Department of Pharmacy, Negelle Health Science College, Guji, Ethiopia.

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***Corresponding Author:** Gudisa Bereda, Department of Pharmacy, Negelle Health Science College, Guji, Ethiopia.
Tel: +251913118492/+251919622717
E-mail: gudisabareda95@gmail.com

Abstract

Rheumatic diseases, because of their systemic inflammatory component, are associated with several shared comorbidities. The high affinity of shared epitope for citrullinated peptides could accelerate the amount of human leukocyte antigen peptide complexes on the surface of antigen-presenting cells, thus leading to a (possible joint-specific) T- cell response. Molecules such as receptor activator of nuclear factor κB ligand, prostaglandins, and matrix metalloproteinases are induced by pro-inflammatory cytokines, involving tumor necrosis factor and interleukin -6, and mediate signs and symptoms of the disease, involving pain and swelling, and degradation of cartilage and bone. Steroids at dosages equivalent to less than 10 mg of prednisone daily are highly effective for relieving symptoms of rheumatoid arthritis and can slow joint injury.

Keywords: Management; pathophysiology, rheumatic disease; risk factors.

Abbreviations

ARA: American Rheumatism Association; ACPA: Anti-citrullinated Protein Antibodies; AMPA: Anti-posttranslationally Modified Protein Antibodies; APCs: Antigen-presenting Cells; CVD: Cardiovascular Disease; DMARDs: Disease-modifying Antirheumatic Drugs; HLA: Human Leukocyte Antigen; IL: Interleukin; NSAID: Nonsteroidal Anti-inflammatory Drug; PAD-2: Peptidyl-arginine deaminase-2; RA: Rheumatoid Arthritis; RANKL: Receptor Activator Of Nuclear Factor κB ligand; RF: Rheumatoid Factor; SE: Shared Epitope; TNF: Tumor Necrosis Factor.

Introduction

Rheumatoid arthritis (RA) is a symmetric polyarticular arthritis that initially affects the small diarthrodial joints of the hands and feet. In addition to inflammation in the synovium, which is the joint lining, the aggressive front of tissue called pannus invades and destroys local articular structures [1, 2]. Rheumatoid arthritis is the most frequent inflammatory arthritis, affecting 0.8 percent of the adult population worldwide. Onset frequently occurs between 30 and 50 years of age [3]. RA is frequently complicated by elevated atherosclerosis and accelerated CVD risk. Rheumatic diseases, because of their systemic inflammatory component, are associated with several shared comorbidities [4]. Several autoantibodies can be detected in serum of RA patients, of which rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are the most prominent [5]. RA typically presents as a symmetric polyarthritis, affecting more women than men and is linked with the presence of autoantibodies in the serum such as anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) [6].

Risk factors

Smoking: Of the environmental risk factors for (anti-citrullinated protein antibodies (ACPA)-positive) RA, smoking is the most significant. Several theories exist on how smoking might predispose to RA. Smoking leads to higher expression of the peptidyl-arginine deaminase-2 (PAD-2) enzyme, accelerating the level of citrullination in the lung [7].

Genetic risk factors: Several environmental and genetic risk factors elevating disease susceptibility have been distinguished. Twin studies have revealed that genetic variation accounts for 50 to 60% of the risk on RA development. The high affinity of shared epitope (SE) for citrullinated peptides could accelerate the amount of human leukocyte antigen (HLA) peptide complexes on the surface of antigen-presenting cells (APCs), thus leading to a (possible joint-specific) T cell response [8, 9].

Autoantibodies in RA: It is estimated that 50–80% of RA pa-

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tients harbors autoantibodies. The presence of autoantibodies has permitted the identification of subgroups of RA patients that are not only more homogenous with regard to risk factors but also regarding the clinical disease course. RF, an autoantibody directed against the Fc part of human IgG, was the first autoantibody system to be explained in RA. Seropositive RA is associated with accelerated radiographic progression and joint injury, while seronegative RA patients have higher inflammation parameters at presentation [10-12].

The microbiome: RA patients can be distinguished from healthy controls based on alterations and dysbiosis of the microbiome, for example, regarding clostridium, lactobacillus, and bifidobacteria species in the gut microbiota. Some bacterial cell wall components might molecularly mimic human autoantigens, triggering an immune response also directed against the joint [13]. The bacterium Porphyromonas gingivalis, causing severe periodontitis, might provide a pathophysiological explanation for this epidemiological relation, since ACPAs can bind citrullinated alpha-enolase of P. gingivalis. Additionally, this microorganism expresses a PAD enzyme, providing a source of citrullinated antigens in a pro-inflammatory environment [14, 15].

Anti-citrullinated protein antibodies: Citrullinated peptides are produced in response to a posttranslational modification mediated by PAD enzymes. Multiple antibody isotypes involving IgG, IgA, and IgM directed against these citrullinated peptides are detected in RA. The presence of ACPA IgA is in line with the hypothesis that ACPA is related to smoking or microbiome dysbiosis, as IgA is related to a mucosal origin of the immune response. Synovial fluid from inflamed RA joints contains citrullinated proteins, suggesting that ACPA could bind to these antigens in the joint and possibly accelerate local inflammation [16].

Anti-acetylated protein antibodies: The latest addition to AMPAs in RA patients is anti-acetylated protein antibodies which have been explained in approximately 40% of RA patients, mainly in the ACPA-positive group. Detection rates in seronegative RA patients were comparable to patients with resolving arthritis, rendering it improbably that these antibodies will be a new biomarker helpful for diagnosing RA [17].

Anti-carbamylated protein antibodies: Anti-carbamylated protein (anti-CarP) antibodies also belong to the group of anti-posttranslationally modified protein antibodies (AMPA) that have been explained in RA. Carbamylation is a chemical reaction mediated by cyanide in which a lysine is converted into a homocitrulline. Certain conditions, for example, renal disease, smoking, and inflammation can accelerate cyanide levels and thus Carbamylation [20, 21].

The Pathophysiology of rheumatoid arthritis

Although the etiology of RA remains elusive, susceptibility factors are evident. Thus, the threefold predominance of RA in women perhaps attributable to hormonal factors, and the clear-cut genetic contribution in this disease is contained predominantly within the HLA class II locus. RA is described by infiltration of the synovial membrane in multiple joints with T cells, B cells, and monocytes. This process is preceded by activation of endothelial cells; neovascularization (growth of new blood vessels) is another hallmark of RA synovitis. Expansion of synovial fibroblast-like and macrophage-like cells leads to a hyperplastic synovial lining layer. This expanded synovial membrane, often termed "pannus," invades the periarticular bone at the cartilage-bone junction and leads to bony erosions and cartilage degradation [22-26]. Molecules such as receptor activator of nuclear factor κB ligand (RANKL), prostaglandins, and matrix metalloproteinases are initiated by pro-inflammatory cytokines, involving tumor necrosis factor (TNF) and interleukin (IL)-6, and mediate signs and symptoms of the disease, involving pain and swelling, and degradation of cartilage and bone. Stimulation by RANKL, TNF, and IL-6 generates osteoclasts within the synovial membrane and promotes bony injury. These molecular and cellular events result in the clinical disease expression. Progression of joint injury is intrinsically associated with joint swelling [27,28].

Diagnostic criteria

In clinical trials, rheumatoid arthritis is diagnosed formally using seven American Rheumatism Association (ARA) criteria. In typical outpatient practice, a definitive diagnosis using these criteria may be difficult to obtain early in the disease process. During the primary visit, patients should be asked about degree of pain, duration of stiffness and fatigue, and functional limitations [29,30].

Treatment

Joint destruction in rheumatoid arthritis commences within a few weeks of symptom onset; early treatment reduces the rate of disease progression.Therapeutic objectives involve preservation of function and quality of life, minimization of pain and inflammation, joint protection, and control of systemic complications [31].

Pharmacological management

Pharmacotherapy for rheumatoid arthritis generally includes a nonsteroidal anti-inflammatory drug (NSAID) for control of pain, with selective use of low-dose oral or intra-articular glucocorticoids, and initiation of a DMARD [32].

NSAIDs: NSAIDs, salicylates, or cyclooxygenase-2 inhibitors are used for primary treatment of rheumatoid arthritis to initiate joint pain and swelling. Cyclooxygenase-2 inhibitors must be used with caution, given current findings regarding potential adverse effects [33].

Glucocorticoids: Steroids at dosages equivalent to less than 10 mg of prednisone daily are highly effective for relieving symptoms of rheumatoid arthritis and can slow joint injury. Steroid dosages should be kept at a minimum because of the high risk of side effects, which involve osteoporosis, cataracts, cushingoid symptoms, and abnormalities in blood glucose levels [34, 35].

Disease-Modifying Antirheumatic Drugs (DMARDs): DMARDs should be considered for all patients with rheumatoid arthritis. Compliance, disease severity, physician experience, and the presence of various comorbidities guide medication choice. The most frequently used medications are methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, infliximab, and etanercept. Sulfasalazine or hydroxychloroquine usually are started first, but in more severe cases, methotrexate or combination therapy perhaps first-line treatment. Enhancing evidence indicates that combinations of DMARDs can be more effective than single-drug regimens [36]. Gold compounds belong to the class of drugs called disease-modifying antirheumatic drugs (DMARDs). The target molecules of DMARDs, involving gold compounds, D-penicillamine, sulfasalazine, bucillamine, and actarit, have not been clearly distinguished, but the targets of methotrexate, leflunomide, mizoribine, and tacrolimus have been well defined. Now there is a new class of drugs, involving protein kinase inhibitors, which target unique molecules that regulate cell functions [37]. Traditional DMARDs are found to have several benefits. They ameliorate the signs and symptoms of RA, decrease inflammation, ameliorate functional/disability status in comparison with non-steroidal antiinflammatory drugs (NSAIDs) in early RA, slow down radiographic progression, provide dosing flexibility, and have well studied and quantified toxicity and drug interaction profiles. However, they also have several significant limitations. They have a delayed onset of action (1–6 months in most cases); some have less approved effectiveness on radiographic disease progression and health related quality of life; require close monitoring because of multiple toxicities; provide for difficult and complex dosing regimens; provide limited long term sustainability; and seldom yield treatment free remissions [38].

Newer DMARDs: Several new drugs with novel mechanisms of action have emerged in current years, involving leflunomide, tumor necrosis factor (TNF) antagonists, and anakinra. Leflunomide is a competitive inhibitor of an intracellular enzyme needed for de novo pyrimidine synthesis by activated lymphocytes [39, 40]. TNF antagonists lower the levels of TNF-a, which is present in accelerated concentrations in the synovial fluid in patients with rheumatoid arthritis. Infliximab, another TNF antagonist, is a chimeric IgG1 anti–TNF-α antibody.Methotrexate is significant for several reasons. First, a large proportion of patients (≈25%-40%) importantly ameliorate with methotrexate monotherapy, and in combination with glucocorticoids almost half of patients can attain low disease activity or remission in early RA, a rate identical to that achieved with biologic DMARDs. Second, its adverse events are well known and many, such as nausea, hair loss, stomatitis, and hepatotoxicity, can be prevented by prophylactic use of folates (folic acid at 1 mg/d or 10 mg/wk). Third, targeted DMARDs, biologic and synthetic, have fewer efficacies as monotherapies than when combined with methotrexate [41,42].

Conclusion

Rheumatoid arthritis (RA) is a symmetric polyarticular arthritis that initially affects the small diarthrodial joints of the hands and feet. Smoking leads to higher expression of the peptidylarginine deaminase-2 (PAD-2) enzyme, increasing the level of citrullination in the lung. Expansion of synovial fibroblast-like and macrophage-like cells leads to a hyperplastic synovial lining layer. Pharmacotherapy for rheumatoid arthritis generally includes a nonsteroidal anti-inflammatory drug (NSAID) for control of pain, with selective use of low-dose oral or intra-articular glucocorticoids, and initiation of a DMARD.

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