Rheumatoid Arthritis: A Brief Overview of Pathogenesis with Associated Risk Factors and Clinical Treatment

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease that is characterized by joint pain, stiffness, and swelling. The etiology of Rheumatoid arthritis is unknown, however according to medical reports and studies, the main factors that contribute to the development of RA include the genetic and individual risk factors or prolonged exposure to environmental triggers. In the development of RA a key role is played by the T cells, B cells and the concurrent interactions of the pro-inflammatory factors. Rheumatoid arthritis (RA) was regarded as a major clinical problem, however treatments involving biologics have revolutionized the management of this inflammatory disease. In RA the underlying objective of using therapeutics is to reduce the activity of this disease with the main aim focussing on disease remission. In order to develop novel treatment for RA, a range of strategies needs to be developed which primarily shall focus on those patients who do not respond to available drugs, including biologics, that are being explored currently. The main aim of writing this review is to give a strong knowledge about the epidemiology, risk factors, clinical manifestations, diagnosis and a few of the many treatment strategies currently being evaluated, which are hoped to lead to greater benefits and better disease management in the clinical setting.

Keywords: Rheumatoid arthritis (RA), risk factors, clinical manifestations, treatment.

I. INTRODUCTION

Rheumatoid arthritis (RA) is an chronic, progressive, inflammatory autoimmune disorder that primarily damages joints and causes destruction of joints and erosion of bones. This disease is characterized by the intrusion of white blood cells into the synovial tissue and synovial fluid of joints, ultimately causing destruction to bone cartilage (Estelle et al., 2005). In the synovial tissue, these leukocytes along with other cells particularly RA synovial tissue fibroblasts, produce factors of inflammation, including chemokines (Szekanecz et al., 2003). According to worldwide studies rheumatoid arthritis (RA) is a most common autoimmune disease that affects 0.5% to 2.0% of the human population (wang et al., 2015 and Korczowska 2015). Further advancement of RA leads to joint destruction, functional disability, and sometimes death.( McInnes and Schett 2011; Huang et al., 2014). RA affects more women than men (female to male ratio 3:1) and prevalence increases with age, most commonly presenting between 50 and 70 years of age.( Symmons et al., 1994). and the morbidity rate of RA in female is 2~3 times higher than male (Hooghof et al., 2016).Among the RA patients, the mortality rate is very high, and different systemic complications such as cardiovascular remain the greatest challenge. Approximately 1% of the RA affected population is associated with increased morbidity and mortality rates.( Kaplan 2010). Effective treatment of RA has been impeded by a paucity of accurate diagnostic and prognostic tests, owing in part to the heterogeneity of the disease. The progression of this disease can be slowed down with adequate medical control; however, this condition remains as one of the
most important cause of inability and disability if not properly treated.

II. Epidemiology

RA influences roughly 1% of the population around the world. In the most recent years, a few epidemiological investigations of RA have been distributed, indicating varieties in the frequency and pervasiveness of RA crosswise over populations. The majority of the investigations have been created in nations from the North Europe and North America, evaluating prevalences of 0.5–1.1%. (Tobón et al., 2010). Another investigation made for the most part in nations from South Europe revealed bring down pervasiveness around 0.3–0.7%. (Carmona et al., 2002 and Guillemin et al., 2005). The most reduced pervasiveness information have been accounted for in zones from Africa and Asia, and the most noteworthy in Native American populations. Truth be told, the pervasiveness of RA is 10 times higher among Canadian or Native Americans than Europeans (3% and 0.3%, separately). (Molokhia and McKeigue 2000) (El-Gabalawy et al., 2011)

III. Pathogenesis

Although the exact cause for the development of rheumatoid arthritis is unknown but a number of medical studies and reports have suggested a number of factors . These factors not only involve the genetic but also environmental factors are considered contributory to the progression of this disease. While etiology of rheumatoid arthritis is unknown, medical evidences suggest that RA develops more often in individuals with inherited genetic and individual risk factors or exposed to environmental trigger (Krzysztof et al., 2015). Rheumatoid arthritis involves a complex interplay among genotype, environmental triggers, and chance. ( Iain et al., 2011)

Genetic Factors

Genome-wide association studies have identified greater than 100 percent genetic susceptibility loci associated with RA, many of which are commonly present in the general population (Okada et al., 2014). The long-established association with the human leukocyte antigen (HLA)-DRB1 locus has been confirmed in patients who are positive for rheumatoid factor or ACPA; alleles that contain a common amino acid motif (QKRAA) in the HLA DRB1 region, termed the shared epitope, confer particular susceptibility. (Gregersen et al., 1987). Candidate gene approaches, genome-wide association studies (GWAS), and trans-ethnic GWAS meta-analyses have identified a number of RA risk genes, such as HLA-DRB1, PTPN22, STAT4, CCR6, TNFAIP3, PADI4, CD40, and FCRL3, many of which are involved in the functions of immune cells, including T cells, B cells, and macrophages (Okada et al., 2014 and Yamamoto et al., 2015).

Environmental Factors

Environmental factors, such as stress, smoking, excessive coffee drinking and the make-up of the microbial population in the bowel, have all been implicated in higher susceptibility to RA. (Rod Hughes 2016). Of the several environmental factors that have been investigated in relation to RA, the evidence implicating cigarette smoking as a risk factor remains by far the most robust. (Kulveer and Paul 2016). A greater intake of vitamin D reduced the incidence of RA in older woman (Merlino et al., 2004). Exposure to silica through the respiratory tract increased the risk of developing RA (Stolt et al., 2005) Other environmental factors, including high birth weight, obesity, and lower socioeconomic status, have also been found to be associated with a higher risk of RA. Similarly, environmental exposures, such as ultraviolet light and silica dust, have also been linked with increased RA risk. In contrast, lifestyle factors, such as longer duration of breastfeeding and moderate alcohol intake, may be protective (Karlson and Deane 2012; Lahiri et al., 2012). Infectious agents (e.g., Epstein–Barr virus, cytomegalovirus, proteus species, and Escherichia coli) and their products (e.g., heat-shock proteins) have long been linked with rheumatoid arthritis, and although unifying mechanisms remain elusive, some form of molecular mimicry is postulated. ( Kamphuis et al., 2005)

Epigenetic Factors

Several epigenetic mechanisms, including posttranslational histone modifications, DNA methylation, and microRNAs (miRNAs), determine the species chromatin structure, consequently in sequencing gene transcription without altering the DNA sequence itself (Basset et al., 2009). Rheumatoid arthritis serves an example of a chronic inflammatory disorder in which miRNAs modulate the inflammatory process in the
joints, with the potential to serve as biomarkers for both the inflammatory process and the potential for therapeutic response. (Victoria et al., 2012).

IV. Clinical Manifestations

Before the diagnosis of RA many of the symptoms may be present although general symptoms can represent a major problem during the course of RA. Symptoms like Weight loss, fever, prolonged early morning stiffness, fatigue, generalised muscle weakness, low mood, and depression are often responsible for a significant loss in the quality of life of patients. Fatigue is reported in 40–80% of RA patients as their most disabling symptom (Balsamo S et al., 2014). Gradual onset polyarthritis with symmetrical, intermittent and migratory joint involvement, especially in the hands and feet are most typical clinical presentations of RA.

Diagnosis

The diagnosis is based primarily on the clinical history and physical examination with support from selected laboratory tests. RA is diagnosed through its distinctive effects on the joints and in skin, and the diagnosis is reinforced by the presence in serum of the rheumatoid factor (RF), although its presence is not necessary for diagnosis of RA. (Treatment of rheumatoid arthritis and other inflammatory disorders: Sample chapter from Biological Therapeutics) Elevated inflammatory markers, such as CRP and ESR, are usually found in association with RA, but may be normal in some people, especially early in the disease. When a patient presents with early arthritis (EA), a quick and definite diagnosis is needed to initiate early treatment. Antinuclear antibodies (ANA) and anti-double-stranded (anti-ds) DNA antibodies may be present in patient with RA (Yukawa et al., 2011). For the early-stage diagnosis and typing of arthritic disease a mixture of oxidized, nitrated and glycated amino acids combined with hydroxyproline and anti-CCP antibody status provided a plasma-based biochemical test because of its high sensitivity and specificity (Usman Ahmed 2016). The early start of disease-modifying antirheumatic drugs (DMARDs) may improve clinical and radiographic outcomes. 1–5 A diagnosis of EA may involve several steps, from the detection and confirmation of arthritis to the final diagnosis by a rheumatologist (Charlotte et al., 2017).

RA are often characterized by the presence of autoantibodies. Rheumatoid factor is not a specific marker for detecting RA as it may be present in patients with other diseases, such as hepatitis C, and in healthy older persons. Anti-citrullinated protein antibody is more specific for RA and may play a role in disease pathogenesis (Balsa et al., 2010). According to the studies of Scott et al., 2010 near about 50 to 80 percent of persons with RA have rheumatoid factor, anti-citrullinated protein antibody, or both in them. A positive antinuclear antibody test is found in patients with RA and the test is of prognostic importance in juvenile forms of this disease. 19 C-reactive protein levels and erythrocyte sedimentation rate are often increased with active RA, and these acute phase reactants are part of the new RA classification criteria (Aletaha et al., 2010).

V. Treatment

Rheumatoid arthritis (RA) is a progressive chronic disease whose treatment is still often symptomatically driven, mainly as a result of incomplete characterization of the underlying disease process. Currently, there is no preventive treatment or cure for RA. However, exciting advances in the understanding of rheumatoid arthritis (RA) and its pathogenesis are providing new hope for those suffering from this debilitating disease. The primary treatment is usually disease-modifying anti-rheumatic drugs (DMARDs), which reduce synovitis and systemic inflammation. Presently, treatment options for RA include glucocorticoids (systemic or intraarticular), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDS) and biologics (bDMARDs). Methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) and leflunomide (LEF) are considered csDMARDS. Biologics include tumor necrosis factor inhibitors like infliximab, adalimumab, etanercept, certolizumab, and golimumab. New biologics include abatacept, rituximab and tocilizumab (Berkant Avci et al., 2015). Many of the past and current therapies offer little more than symptomatic relief. Even the so-called disease modifying antirheumatic drugs (DMARDs) do not halt the progression of this disease, but rather decrease the onset of disability by 30% (Ann Pittier 2000).
Treatment Alternatives
As the side effects of synthetic drugs are common and usually unavoidable, new experiments search for naturally derived therapeutic medications such as bovine lactoferrin, which has anti-inflammatory properties (Smolen et al., 2014). Diverse strategies to develop novel treatments for rheumatoid arthritis which specifically target those patients who do not respond to available medications, including biologics, are currently being explored. New potential therapeutic approaches which may become available as part of standard therapeutic regimens include the propagation of regulatory T cells and—in the future—of regulatory B cells. New biologic disease-modifying antirheumatic drugs (b-DMARDs) against interleukin-17 and -6, granulocyte-macrophage colony-stimulating factor, and complement component 5 are now standard components of clinical treatment programs. In addition, recent data indicate that bispecific monoclonal antibody therapies may be more effective than monoclonal antibody monotherapies. It is also becoming apparent that the use of more toxic b-DMARDs against B cells, a therapeutic strategy already being applied in the treatment of haematological diseases, may also be efficacious for treating B cell-mediated autoimmune diseases. Undoubtedly, more small molecules will be developed in the future, and combination therapies with, for example, kinase inhibitors and b-DMARDs, will most likely be tested. Finally, immunoproteasome inhibitors will become available for patients with B cell-mediated autoimmunities, which are refractory to currently available treatment options. The new and exciting extension of current treatment options for rheumatoid arthritis, biosimilars, will not be discussed in this review as details on these agents are available in recently published reports (Joachim, 2016).

Use of herbal medicine in treating RA is becoming more and more popular due to their negligible toxic effects and rare side effects. Studies by Ankit Anwar et al., 2017 have identified many natural plant products with significant therapeutic potential against RA. These plant products might be responsible for relieving inflammation and reducing the symptoms of the disease. The employment of stem cells to treat rheumatoid arthritis, a debilitating and even life-threatening condition, has the potential to drastically improve the quality of life of sufferers by a factor which cannot be provided by current therapies or medicines, and even provide a route to a lifelong cure, for which there is currently no option available (Medlink and Vet-Medlink 2014).

VI. Conclusion
Rheumatoid arthritis can be a painful and disabling condition and if it is not properly treated it could result in significant disability. Over the past 25 years there has been profound advances in the treatment of RA. With the availability of medications it is now possible to slow or halt the progression of the disease and prevent the tissue damage. In addition to medications, it is necessary to incorporate pharmacologic and surgical interventions which are important elements of care for RA. It is thus very necessary and important to identify potential clinical biomarkers that will prove helpful in the management and treatment of this disease. It is possible to identify a series of biologic and small molecules agents in order to detect the onset of rheumatoid arthritis, however much of this mystery needs to be resolved. Further we need to understand the factors that lead to loss of tolerance, find ways to enhance immunologic resolution or homeostasis and repair of damaged joints. Also we must understand the basic mechanisms which drive the onset of these systemic disorders and should develop such curative and preventive ameliorative regimens that will transform the notion of rheumatoid arthritis as a chronic disease in order to improve the quality and strength of life.

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