EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 5
948-952
Year: 2018

RHEUMATOID ARTHRITIS: AN OVERVIEW

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Article Received on 19/03/2018 **Article Revised on 09/04/2018** **Article Accepted on 30/04/2018**

ABSTRACT
Purpose of Review: Rheumatoid arthritis is a chronic inflammatory disease in which early aggressive therapy with disease-modifying antirheumatic drugs can improve outcome and prevent joint damage. While such therapy is effective, its application can be limited by diagnostic uncertainty in patients with early inflammatory arthritis and concerns about treatment of patients whose disease would remit spontaneously. The purpose of current research is therefore to identify prognostic markers of early disease and to determine the role of aggressive treatment strategies in inducing remission in such patients. **Recent Findings:** Recent research has provided new information on genetic markers predicting rapid progression of joint destruction; the role of serology, in particularly, antibodies to citrullinated peptides in diagnosing rheumatoid arthritis; the utility of radiographic techniques in detecting both early synovitis and bone erosion; and the value of combination therapy in controlling signs, symptoms and radiographic progression. Recent clinical studies support the efficacy of a combination of methotrexate with a biological agent, especially a tumor-necrosis-factor blocker, in reducing disease activity. **Summary:** While current treatment approaches can produce significant benefits in patients with early arthritis, future investigation is needed to target therapy more selectively and to determine which patients respond best to various agents or combinations.

KEYWORD: Rheumatoid arthritis antirheumatic synovitis or combinations.

INTRODUCTION
RA is a disease where your immune system mistakenly targets your own body. It especially affects the lining of the joints between your bones. Early symptoms include swelling, heat, tenderness, pain or stiffness in your joints. In some cases, when the swelling goes down, the joint capsule remains stretched and can no longer hold the joint in its proper position. As a result the joint becomes unstable and this can lead to joint damage. The extent to which this happens varies a great deal from person to person. Most people with RA have some damage in a number of joints, and a few have quite severe damage in a lot of joints.[1]

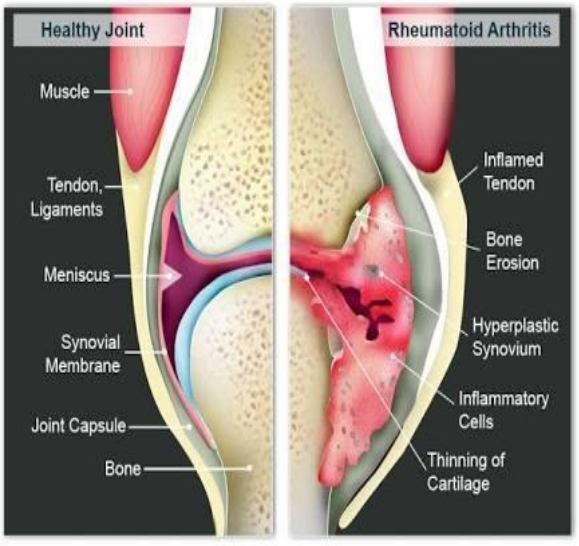

Fig 1: Difference of healthy joint and rheumatoid arthritis.

CAUSES
Doctors don't know the exact cause of rheumatoid arthritis. They know that with this arthritis, a person's immune system attacks his or her own body tissues.

Researchers are learning many things about why and how this happens. Things that may cause rheumatoid arthritis are:

- Genes (passed from parent to child).
- Environment.
- Hormones[2]

Symptoms

The principal symptom of rheumatoid arthritis (RA) is inflammation of the joints. Inflammation may also occur in other tissues, including, for example, the heart, lungs, kidneys and pleura. RA is systemic in that it may attack several different joints, and in many cases appears to affect different joints at different times, hence the term 'migratory or flitting polyarthritis' used by some authorities. Over time, irreparable damage is done to the joint due to inflammation of the synovial membrane, which forms the lining of the tendon sheaths and the joints. As the disease progresses, it destroys the joint tissues and reduces joint mobility through, for example, erosion and tethering of the tendons. This means that the tendon becomes fixed to adjacent tissues, which restricts its movement. Eventually, use of joints in the hands and limbs is lost, and fingers and toes may become severely deformed. In the skin, subcutaneous nodules form, and vasculitis may also be diagnosed, which is the chronic destruction of blood vessels. Several other haematological, radiological and biochemical tests are used to confirm the diagnosis but are not dealt with here. RA has traditionally been associated with morbidity and significantly earlier mortality.[5]

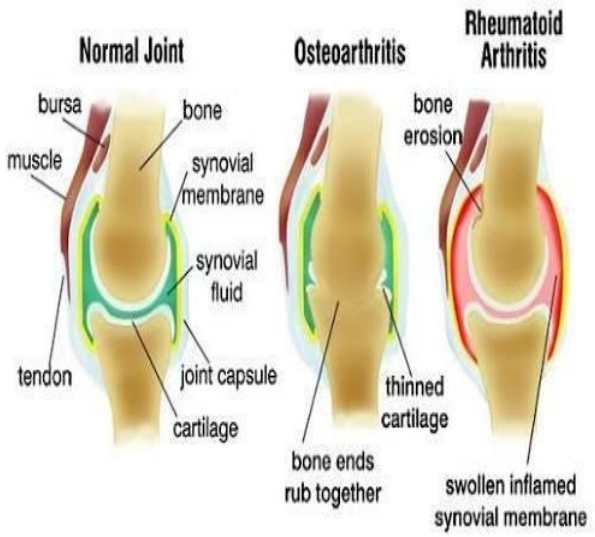

Fig. 2: Symptoms of rheumatoid arthritis.

Diagnosis of rheumatoid arthritis – clinical criteria

The criteria listed below are those published by the American College of Rheumatology in 1987. Any four of the criteria listed below must be identified for positive diagnosis of RA:

* Detection of serum RF
* Morning stiffness for 1 hour or longer for 6 weeks or more
* Arthritis in three or more joints persisting for 6 weeks or more
* Persistence for 6 weeks or more of symmetrical arthritis
* Persistence for 6 weeks or more of arthritis of the hand joints
* Rheumatoid nodules observation, using hand radiographs, of changes, erosion or unequivocal bony decalcification.

Current aims of treatment of RA

* Slow the rate of disease progression.
* Control inflammation and pain; ideally the patients should be as free as possible from pain.
* Design the appropriate treatment regimen for each patient.
* Regular appointments with the clinic and the rheumatologist.
* Regular patient monitoring for adverse effects of treatments.
* Regular blood tests.
* Monitor patient compliance[3-4]

Certain Types of Arthritis

Most people are familiar with the term arthritis. But many people may mistake RA for certain other types of arthritis. Even though the symptoms may seem the same, the diseases are quite different. Getting an appropriate treatment plan for RA depends on getting an accurate diagnosis as early as possible. Only a doctor can determine whether you have RA or another type of arthritis.

	Rheumatoid Arthritis	Osteoarthritis	Psoriatic Arthritis	Ankylosing
Type of Disease	Autoimmune arthritis	Known as the "wear and tear" type of arthritis and is associated with factors such as aging, injury, or obesity	A type of autoimmune arthritis associated with psoriasis (a disease that causes red, scaly patches on the skin)	A type of autoimmune arthritis that mostly affects the back and hips
Symptoms	Joint pain, swelling, and stiffness; decreased range of motion; fever, fatigue, and loss of energy can also occur	Joint pain, swelling, and stiffness; decreased range of motion; fever, fatigue, and loss of energy can also occur	Joint pain, swelling, and stiffness, as well as tenderness or pain where tendons or ligaments attach to bones. Red, scaly patches of skin often on the elbows, knees, and scalp	Low back pain and stiffness, as well as tenderness or pain where tendons or ligaments attach to bones
Location of Symptoms	Often causes swelling in pairs of joints— especially smaller ones (both hands, both ankles, etc.)	Usually affects weight-bearing joints (ie, back, hip, knee) as well as the neck, small finger joints, and big toe	Usually affects the ankles, knees, fingers, toes, and lower back	Mostly affects the joints of the spine andalso where the spine attaches to the hips
Time of Day	Generally worse in the morning or after long rest and lack of activity	Tends to get worse with activity throughout the day	Tends to be worse in the morning or after a period of rest	Usually worse aftera period of rest or after waking in the morning and may also improve with exercise
Age of Onset	Usually occurs between 30 and 60 years of age, though can occur at any age	Most commonly affects middle- aged and older people	Usually occurs between 30 and 55 years of age. Skin symptoms often appear first	Most often begins from the late teens to 35 years
Prevalence	Approximately 1.3 million people have RA in the US	An estimated 27 million people have osteoarthritis in the US	Between 6% and42% of all people in the US with psoriasis have psoriatic arthritis	An estimated 0.2% of people in the US have ankylosing spondylitis

Management

Early recognition of symptoms and diagnosis is key to a more successful patient outcome. Early review allows faster initiation of treatment and suppression of inflammation. Studies have clearly demonstrated that response to DMARD therapy is related to duration of symptoms prior to diagnosis.

The diagnosis of rheumatoid arthritis can be made with normal autoantibodies/inflammatory markers. Primary care physicians should not wait for investigation results prior to referral if rheumatoid arthritis is suspected. Early referral to a specialist rheumatology clinic has been associated with better results.

Primary care

When patients present with joint symptoms suggestive of inflammatory arthritis, initial treatment by primary care should focus on analgesia. This can include paracetamol, codeine or compound analgesics. Standard NSAIDs or selective COX-2 inhibitors are also options in primary care. Corticosteroids should only be initiated in secondary care after review.

Multidisciplinary care

The management of rheumatoid arthritis involves a multidisciplinary approach through a rheumatology clinic (occupational therapy, physiotherapy, psychology and patient support) along with patient education.

The following professionals may be involved in the care of patients with rheumatoid arthritis as part of the multidisciplinary team:

- Occupational therapist – Help with everyday activities; splints, wrist supports, pacing advice
- Physiotherapist – Specific muscle/joint functioning, eccentric concentric exercise programmes[6]

Treatment

After RA has been diagnosed and an initial evaluation performed, treatment should begin. Recent guidelines have addressed the management of RA, 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 extra-articular manifestations. Disease-modifying antirheumatic drugs (DMARDs) are the mainstay of RA therapy.

DMARDS

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 is recommended as the first-line treatment in patients with active RA, unless contraindicated or not tolerated. 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). Combination therapy with two or more DMARDs is more effective than monotherapy; however, adverse effects may also be greater. If RA is not well controlled with a nonbiologic DMARD, a biologic DMARD should be initiated. 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.

NSAIDS AND CORTICOSTEROIDS

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.

Table 3. Biologic and Nonbiologic Disease-Modifying Antirheumatic Drugs.

Drug*	***Mechanism for rheumatoid arthritis***	***Adverse effects***	***Monthly cost†***
Nonbiologic More commonly used Methotrexate	Inhibits dihydrofolate reductase	Liver effects, teratogenesis, hair loss, oral ulcers	$
Leflunomide (Arava)	Inhibits pyrimidine synthesis	Liver effects, gastrointestinal effects, teratogenesis	$
Hydroxychloroquine (Plaquenil)	Antimalarial, blocks toll-like receptors	Rare ocular toxicity	$$
Sulfasalazine (Azulfidine)	Folate depletion, other mechanisms unknown	Anemia in G6PD deficiency, gastrointestinal effects	$
Minocycline (Minocin)	Antimicrobial, other mechanisms unknown	Drug-induced lupus erythematosus, *Clostridium difficile* colitis	$
Less commonly used Gold	Inhibits antigen processing,	Skin, heme, renal effects	$$

sodium thiomalate	decreases cytokines (TNF, interleukin-6)		
Penicillamine (Cuprimine)	Chelates metal, other mechanisms unknown	Heme, renal effects	$$
Cyclophosphamide	Nitrogen mustard alkylating agent, cross- links DNA	Infertility, cancer, hemorrhagic cystitis	$$
Cyclosporine (Sandimmune)	Calcineurin inhibitor, decreases interleukin- 2	Hypertension, renal effects, hirsutism	$$
Biologic Anti-TNF agents Adalimumab (Humira)	Anti-TNF-α	TB, opportunistic infection	$$$
Certolizumab pegol (Cimzia)	Anti-TNF-α, pegylated	TB, opportunistic infection	$$$
Etanercept (Enbrel)	Anti-TNF-α, receptor	TB, opportunistic infection	$$$
Golimumab (Simponi)	Anti-TNF-α	TB, opportunistic infection	$$$
Infliximab (Remicade)	Anti-TNF-α	TB, opportunistic infection, infusion reaction	$$$
Other biologic agents Abatacept (Orencia)	Costimulator blocker, cytotoxic T lymphocyte antigen 4	Opportunistic infection	$$$
Anakinra (Kineret)	Anti-interleukin-1 receptor blocker	Opportunistic infection, injection site pain	$$$
Rituximab (Rituxan)	Anti-CD20, eliminates B cells	Infusion reaction, opportunistic infection, progressive multifocal leukoencephalopathy	$$$$
Tocilizumab (Actemra)	Anti-interleukin-6 receptor blocker	Opportunistic infection	$$$

G6PD = glucose-6-phosphate dehydrogenase; TB = tuberculosis; TNF = tumor necrosis factor.

*—Nonbiologic drugs listed in approximate order of priority, biologic drugs listed in alphabetical order.

†—$ = $30 to $100; $$ = $100 to $1,000; $$$ = $1,000 to $5,000; $$$$ = more than $5,000.

Information from reference 23.

CONCLUSION

There is no cure for RA, but treatments can recover symptoms and slow the progress of the disease. Disease-modifying treatment has the best consequences when it is started early and aggressively. The areas of treatment are to minimize symptoms such as pain and swelling, to avert bone deformity (for example, bone erosions visible in X-rays), and to maintain day-to- day functioning. This is principally addressed with disease-modifying antirheumatic drugs (DMARDs); analgesics may be used to help manage pain. RA should mostly be treated with at least one specific anti-rheumatic medication. The use of benzodiazepines (such as diazepam) to treat the pain is not recommended as it does not seem to help and is associated with risks.

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