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Current Pharmaceutical Options for the Treatment of Rheumatoid Arthritis

Abstract *Rheumatoid arthritis is an inflammatory and autoimmune disease that describes the joints' persistent inflammation and tendon sheets' synovial lining. The primary symptoms of rheumatoid arthritis are stiffness, pain, and swelling of peripheral joints. Persistent inflammation results in many systemic and extra-articular manifestations involving many organ systems. Rheumatoid arthritis treatment goals are symptomatic management of pain, stiffness and restricted mobility. NSAIDs are commonly prescribed for people with rheumatoid arthritis. Analgesic effects of NSAIDs are based mainly on the inhibition of COX-enzyme and consequently the production of prostaglandins*

Key Words: Arthritis, Swelling, Inflammation, Treatment Options

Introduction

Arthritis is a condition in which one or more joints become inflamed or swollen. It involves almost a hundred disorders that affect the joints, surrounding tissues, and other connective tissues. Joint pain and stiffness are early types of arthritis, which differ depending on the type, there are many types of arthritis (Faye AH Cooles & John D Isaacs, 2011). Osteoarthritis is the most common form of arthritis. Gout, fibromyalgia, and rheumatoid arthritis are a few of the common rheumatic disorders linked with arthritis Pain, aching, stiffness, and swelling in and around one or more joints are common symptoms of rheumatic conditions. The risk factors may appear gradually or unexpectedly. The immune system and various internal organs of the body may be affected by such rheumatic conditions. Rheumatoid arthritis cause inflammation of joints (F. A. Cooles & J. D. Isaacs, 2011) that affects around 1% of the world adults (Choy, 2012). It is 2-3 times more trashy in women than in men (McInnes & Schett 2011) and start at any age, age factor is not dependent on it. It caused the inflammation of synovial tissues resulting in the pain, stiffness and swelling of the hands, feet, wrists and This persistent inflammation and pain is the primary cause of progressive joint damage resulting in deformities and loss of function (Clements, 2011; Kahlenberg & Fox, 2011; Klarenbeek, Kerstens, Huizinga, Dijkmans, & Allaart, 2010).

The etiology of rheumatoid arthritis is unknown (Smolen & Steiner, 2003). Although its cause remains undetermined, many causes are involved in its progress have been studied over the past two years (Dong, Geoffrey, Jun, & Dong, 2008). It has long been assumed that infectious agents could prompt rheumatoid arthritis, but still, it is not confirmed. Rheumatoid arthritis patients respond favorably to drugs with antibiotic activity or those derived from antibiotics (Silman & Pearson, 2002). There is a significant role of the immune system in the development of rheumatoid arthritis. After initiating rheumatoid arthritis, an injury to the synovial membrane occurs, proceed by the CD4 T cells' infiltration in the synovium. These cells are then activated by antigen cells. These $CD4^+$ cells produce, necrosis factor-α, interleukin-2, interferon-γ tumor, which activates monocytes, macrophages, and fibroblasts. These cells activate neutrophils at the

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cartilage merger site and in synovial exudate, where these cells producing varied cartilage destroying enzymes such as metalloprotease (Zwerina, Redlich, Schett, & Smolen, 2005). Immune cells form lymphoid follicle-like structures within the synovial membrane and produce different antibodies such as rheumatoid factor, antibodies directed against the fc fragment of IgG. These autoantibodies form immune complexes and deposit in the cartilage of rheumatoid arthritis patients (Steiner & Smolen, 2002).

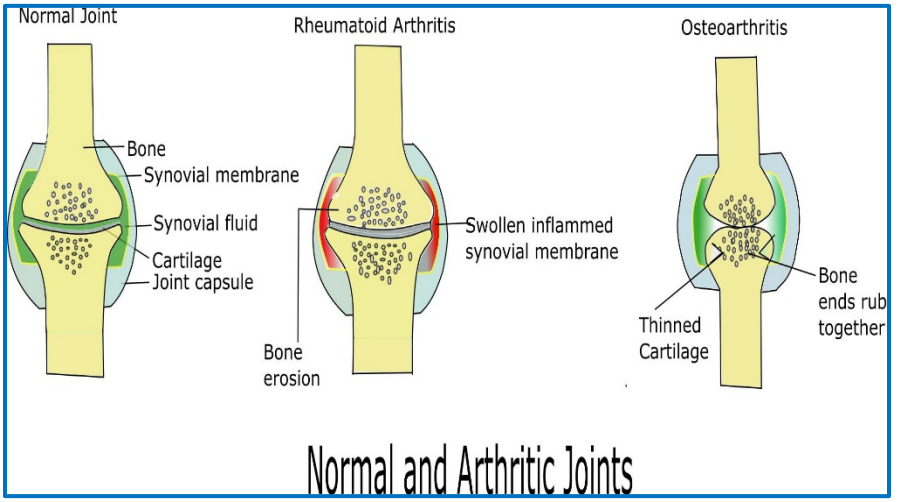

Figure 1: Difference between Normal and Arthritic Joints

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory disease that is highly related to joint destruction and substantial impairment in the quality of life. Persons having family history, women and smokers are mostly affected. The major symptoms of RA are pain and swelling of peripheral joints. RA is mostly nominated as a joints disease however it is also a reason for a variety of extra-articular appearances. A representation of RA is synovial inflammation and its bleakness may differ with disease progression (Quan *et al.*, 2008).

Osteoarthritis

Osteoarthritis is a destructive joint disease caused by the loss of articular cartilage, synovitis and subchondral bone changes resulting in chronic pain, stiffness and disability. Osteoarthritis is the leading cause of disability, with a high prevalence among the aging population and obese persons in Asia. Pain is the main indication in osteoarthritis for which patients visit a doctor. Traditional NSAIDs are more useful for pain management, but adverse effects, including upper gastrointestinal ulceration and hemorrhage, limit their use in osteoarthritis. Celecoxib (selective COX-2 inhibitor) spares COX-1 in therapeutic dosage and provides anti-inflammatory and analgesic effects without increased risk of hematologic adverse effects (Xu, Gu, Yasen, & Hou, 2016).

Dysmenorrhea

Dysmenorrhea, also known as painful menstruation, because of uterine contractions during the menstrual cycle without the pelvic disease. Pain starts at first day of menstruation and is most severe on the first few hours. The underlying cause of dysmenorrhea is the excessive secretion of prostaglandins produced from the COX-2 enzyme. Women with dysmenorrhea have been found to have an increased level of PG growth factor 2 (PGF2). PGF2 stimulates myometrial contractions, sensitization of nerve endings and ischemia. (Daniels, Robbins, West, & Nemeth, 2009).

Ankylosing spondylitis

Ankylosing spondylitis is a severe form of arthritis affecting the spine and is characterized by axial skeletal stiffness and inflammation at the affected site of tendons and ligaments and move towards bone. Common symptoms of Ankylosing spondylitis include pain, fatigue, restricted mobility and stiffness. Although the cause of the Ankylosing spondylitis is not known in 90 % of cases, antigen B27 gene marker of leukocyte is involved. Treatment strategies should include non-pharmacological approaches such as exercise to help maintain the posture.

NSAIDs, including COX-2 inhibitors, are suggested as first-line therapy for patients with pain and stiffness. In 2005 Celecoxib was approved in the USA to treat signs and symptoms associated with Ankylosing spondylitis. Celecoxib effectively relieves pain and improves function in patients with Ankylosing spondylitis in different trials (Walker, Essex, Li, & Park, 2016).

Epidemiology

Arthritis is an inflammatory autoimmune disease (Cooles and Isaacs, 2011, Browning, 2006) that affects approximately 1% of the world adults (Choy, 2012). Women are most commonly affected from arthritis than men (McInnes and Schett 2011) and can occur at any age. It is characterized by the polyarticular inflammation of synovial tissues resulting in the pain, stiffness and swelling of the joints. This inflammation and pain can leads to progressive joint damage resulting in deformities and loss of function (Arden and Nevitt, 2006, Klarenbeek *et al.*, 2010, Kahlenberg and Fox, 2011,Clements, 2011).

Pathophysiology

The etiology of arthritis is unknown (Smolen and Steiner, 2003). Although its cause remains unclear, many pathogenic pathways that are elaborate in its improvement have been studied over the past two decades (Dong *et al.*, 2008). It has long been assumed that arthritis could be prompted by infectious agents, but still it is not confirm. Arthritis patients respond favorably to drugs that have antibiotic activity or those derived from antibiotics (Silman and Pearson, 2002). Osteoarthritis (OA) is a degenerative disorder rising from biochemical breakdown of hyaline in the synovial joints. Osteoarthritis contains not only the articular cartilage but also the entire joint organ, including the subchondral bone and synovium. When the cartilage that cushions the joints crumbles, inflammation occurs. So practically, there is injury which proceeds over a period of time to develop osteoarthritis, initiating the classical symptoms of the disease, including pain, deformity, and ultimately loss of function (Iannone and Lapadula, 2003, Martel-Pelletier, 2004). Immune system has major role in the pathogenesis of rheumatoid arthritis. After initiating the event of rheumatoid arthritis, an injury to the synovial vasculature occurs followed by the infiltration of the CD4 T cells in the synovium. These cells are then activated by antigen presenting cells in connection with the antigens. These $CD4^+$ cells produce interferon-ϒ, interleukin-2, and tumor necrosis factor-α, and, in turn activates monocytes, macrophages and fibroblasts. These cells activate neutrophils at the site of cartilage junction zone and in synovial exudate where these cells produce various cartilage degrading enzymes such as metalloprotease (Zwerina et al., 2005). Immune cells form lymphoid follicle like structures within synovial membrane and produce different autoantibodies such as rheumatoid factor, antibodies directed against the fc fragment of IgG. These autoantibodies form immune complex and deposit in the cartilage of rheumatoid arthritis patients (Steiner and Smolen, 2002).

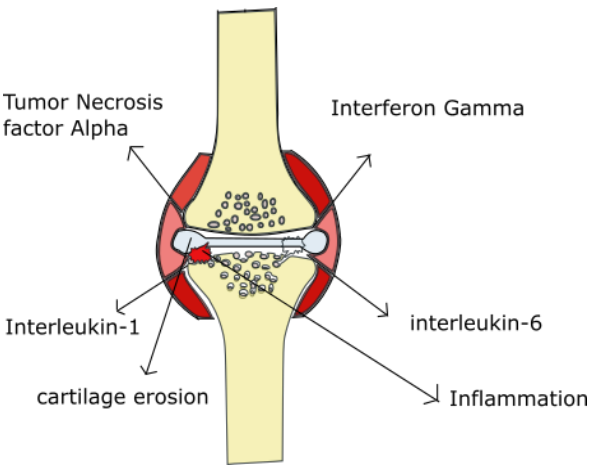

Figure 2: Pathophysiology of Rheumatoid Arthritis

Sign and Symptoms

Arthritics conditions usually involve pain, stiffness, aching and swelling in and around one or more joints. Arthritis mostly disturbs the joints and the symptoms can progress slowly or suddenly. It can cause problems in any joint in the body, though the small joints in the hands and feet are commonly the first to be affected. Arthritis usually affects the joints symmetrically (both sides of the body at the same time and to the same extent), but this isn't always the case certain rheumatic conditions can also include the immune system and various internal organs of the body. Some forms of arthritis, such as rheumatoid arthritis and systemic lupus erythematosus (SLE), can affect multiple organs and cause widespread symptoms (Maini *et al.*, 2004).

Symptoms of osteoarthritis differ greatly with the severity and type of joints. But, the most prevalent symptoms are pain and stiffness, especially after rest or in the morning. Affected joints may get swollen, particularly after lengthy activity. Some symptoms include:

- Stiffness of joints – mostly of the lower back, knees and the hips,
- Limited range of motion or stiffness that goes away after movement
- On joint bending clicking or cracking sound
- Swelling of the joints
- Severe pain after hectic activity (Zhang *et al.*, 2002, Bijlsma *et al.*, 2011)

Table 1. Diagnostic Parameters for Arthritis

Tests	Findings	References
Risk factors	Old age, family history and female sex are connected with amplified risk of RA,	(McInnes and Schett, 2011)
Physical examination	During the physical examination, it is important to assess the following: Stiffness Deformity Tenderness Rheumatoid nodules Pain on motion Swelling Limitation of motion Extra-articular manifestations	(Naredo *et al.*, 2002)
Lab tests	positive antinuclear antibody test result rheumatoid factor test Anti-citrullinated protein antibody test C-reactive protein levels and erythrocyte sedimentation Radiography of hands and feet	(Balsa *et al.*, 2010, Aletaha *et al.*, 2010)

Chronobiology in Rheumatoid Arthritis

An intrinsic, 24hour (circadian) rhythm is a crucial fig ure in the brain and body's cellular and physiological f unctions (16, 17). The role of the circadian clock in ph ysiology is essential for an organism's activity to be s ynchronised with the 24hour environment (18).In rhe umatoid arthritis, chronobiology is important since se vere symptoms including joint pain and stiffness are most noticeable in the morning. In rheumatoid arthriti s patients, the severity of morning stiffness raised pla sma levels of proinflammatory cytokines.Simultaneou sly, healthy people, regardless of the day, have low le vels of cytokines (19).Circadian rhythms are altered in rheumatoid arthritis due to the formulation of core clock gene CRY2 and RORA, proposing a desynchronization of the central clock , and the local synovial clock is altered in respo nse to inflammatory mediators (20).Melatonin levels a re also high in rheumatoid arthritis patients, indicatin g that this hormone has an increased inflammatory ef fect (21). At a systemic level, the circadian clock guide s temporal changes in cytokine secretion and joint sy mptoms through the charge of signalling pathways, a nd at a local level, independent clocks present in infla

mmatory cells guide temporal changes in cytokine se cretion and joint symptoms (18).

Treatment plan

The objectives of the treatment of OA of the knee are to relieve pain, retain or recover mobility, and reduce infirmity. There are numerous strategies on the treatment of OA. They are typically based on the confirmation of the various interferences such as pharmacological and non-pharmacological therapy (Hochberg *et al.*, 2000, Mazières *et al.*, 2001).

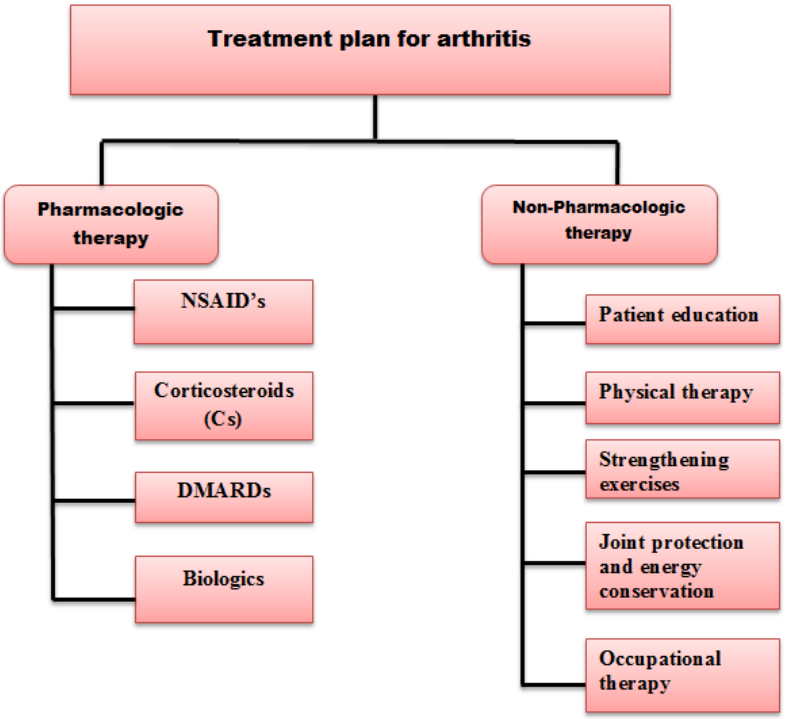

Figure 3: Treatment Options for Arthritis

Pharmaceutical Options for the Treatment of Rheumatoid Arthritis

Various pharmaceutical options are exploited for the treatment of rheumatoid arthritis. In the past two decades, a shift in treatment strategy from the pyramid approach towards disease-modifying antirheumatic drugs has been observed. According to the pyramid approach, treatment is usually started with NSAIDs. If the pyramid approach seems ineffective, it is replaced with DMARDs, distinguished from NSAIDs due to their disease-modifying potential and slow onset of action (Verstappen et al., 2003).

DMARDs

Disease-modifying antirheumatic drugs (DMARDs) go through the basis of the treatment of rheumatoid arthritis in the 1970s. The mechanisim of DMARDs shows that it decrease the inflammation and progression of the disease, but the extent of their effectiveness is variable (Verstappen et al., 2003). A major issue in treating rheumatoid arthritis is selecting the drug because it is not definite which patient will respond to which drug. Patient-specific disease signatures are being developed through the genetic and proteomic approaches to treat rheumatoid arthritis. Practical applications of such advances have not been attained yet. Practice guidelines usually recommend initiation of treatment with conventional DMARDs. Combination therapy of DMARDs is more effective than monotherapy to achieve the desired therapeutic outcomes (Ma, Kingsley, & Scott, 2010). The availability of biological DMARDs has revolutionized rheumatoid arthritis treatment through targeted specific abnormalities of the immune system.

These medications have been shown to play an important role in rheumatoid arthritis pathology. Biologic DMARDs therapy is commonly recommended for the patients who have failed to use mono or combination therapy of conventional DMARDs. However, for patients presenting severe disease symptoms, DMARDs can be optioned as first-line treatment. Biologic DMARDs, each having its toxicity and therapeutic effectiveness. Usually, DMARDs are not used in combination with other drugs, but trials are ongoing to set the combination therapy's risk-benefit ratio (Kahlenberg & Fox, 2011).

Table 2. Treatment guidelines of the American college of Rheumatology (2015)

Drug category	Description
DMARD monotherapy	Most often methotrexate monotherapy, but may also be hydroxychloroquine, leflunomide, sulfasalazine.
Double DMARD therapy	Methotrexate+sulfasalazine, Methotrexate+hydroxychloroquine, sulfasalazine+hydroxychloroquine
Triple DMARD therapy	Methotrexate+sulfasalazine+hydroxychloroquine
DMARD combination therapy	Double or triple conventional DMARD therapy
Biologics	
TNFi biologics	Adalimumab, etanercept, golimumab, or infliximab
Non-TNF biologics	Abatacept, rituximab, tocilizumab
Low dose glucocorticoids	<10mg/day of prednisone
High dose glucocorticoids	>10mg/day of prednisone
Short term glucocorticoid	< 3month treatment

NSAID's

Conventionally, nonsteroidal anti-inflammatory drugs (NSAIDs) have been the drug of choice for treating pain in patients with RA and osteoarthritis and offer quick aid from symptoms. (NSAIDs) shows antipyretic, anti-inflammatory, analgesic, effects. As Rheumatoid arthritis is inflammation disease of joints, drugs which can reduce the inflammation, such as glucocorticoids and NSAIDs are used as an initial therapy (Maqbool et al., 2020). Nonsteroidal anti-inflammatory drugs (NSAIDs) worked as a support therapy until the slow-acting disease-modifying antirheumatic drugs (DMARDs) used become beneficial because these drugs can successfully relieve stiffness and pain at RA. (NSAIDs) always used in combination in deep-rooted RA since they have not been found to slow the disease's clinical or radiographic development (Fidahic, Jelicic Kadic, Radic, & Puljak, 2017; O'dell, 2004).

NSAIDs switch pain and inflammation by inhibiting cyclooxygenase 1 and 2 (COX 1 and COX 2) enzymes. However, inhibition of the COX 1 enzyme is cause GIT toxicity. NSAIDs causes stomach and intestinal ulcers, which sometimes rupture and bleed and causing death (Bhatt et al., 2008). Approximations of the number of deaths due to NSAID-related GIT bleeding fluctuate frequently and data of approx. 3500 to 16.500 per year are cited for the US in a FDA report (van Laar et al., 2012). High blood pressure and increased cardiovascular risk are associated with conventional NSAIDs and COX-2 inhibitors (Friedewald et al., 2010). Of all NSAIDs, naproxen implements the least cardiovascular risks, though naproxen is linked with the same risk for causing heart problems as other NSAIDs (Kearney et al., 2006).

Recent epidemiological research on NSAIDs has clearly shows that prolonged use together a diminished risk of cancer. At the same time, clinical and preclinical have demonstrated their effectiveness in preventing and treating cancer (Futagami et al., 2007). This effect mainly holds concerning stomach, colon and rectal cancer. Various mechanisms have been suggested to explain NSAIDs' anti-tumor action, including cell growth suppression, inhibition of angiogenesis, and metastasis and NSAIDs induced cancer cell apoptosis (Kısmet, Akay, Abbasoğlu, & Ercan, 2004). COX-2 enzymes in the gastric cancer cells are believed to play a critical role in gastric carcinogenesis (Hu et al., 2004).

Corticosteroids (Cs)

Glucocorticoids (GCs) are a form of corticosteroid that has powerful anti-inflammatory and immunosuppressive effects, which is why they are commonly used in RA. About half of rheumatoid arthritis patients are expected to be treated with glucocorticoids on a long-term basis (32).

Glucocorticoids (GCs) are a class of steroidal hormones that bind to cortisol receptors and cause a variety of biological effects. In addition to understanding anti-inflammatory and immunosuppressive properties with short and medium-term use, long-term treatment with low-dose glucocorticoids will greatly reduce the degree of erosion progression in RA. Low-dose glucocorticoids are used as a supportive treatm ent to help control the symptoms while
DMARDs or biological agents are being produced.GC monotherapy isn't recommended right now (33).

Conclusion

Rheumatoid arthritis is an autoimmune disease that causes inflammation. Rheumatoid arthritis has no known cause. In rheumatoid arthritis, the function of the circadian clock is critical. Rheumatoid arthritis treatment involves: Disease-modifying antirheumatic drugs (DMARDs), Non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids (GCs) have potent anti-inflammatory and immunosuppressive properties. Osteoarthritis is a destructive joint disease characterized by loss of articular cartilage, synovitis and subchondral bone changes resulting in chronic pain, stiffness and disability. High prevalence among the aging population and obese persons. NSAIDs are more useful for pain management. Ankylosing spondylitis is a form of arthritis that affects the spine over time. Pressure, fatigue, restricted mobility, and stiffness are all symptoms of ankylosing spondylitis. Patients with pain and discomfort are treated with nonsteroidal anti-inflammatory drugs (NSAIDs).

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