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Research Article

Rheumatoid Arthritis and Drugs Management

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Abstract

Rheumatoid Arthritis (RA) typically begins with symptoms such as fatigue, stiffness, and musculoskeletal pain, which may take weeks to months to develop into joint involvement. Initially, the small joints are primarily affected, especially the small bones in the hands. Subsequently, larger joints become involved, leading to swelling, warmth, and pain. Morning stiffness or stiffness following periods of inactivity are indicative of active RA. Patients often report experiencing slowness or difficulty in movement when rising from bed or after remaining in a single position for an extended duration. This review is based on research studies indexed in Scopus, Science Direct, PubMed, and Google Scholar databases. Rheumatoid arthritis is an autoimmune inflammatory condition mainly distinguished by synovitis, which is often associated with the involvement of extra-articular organs, such as interstitial pneumonia. This condition also presents clinical symptoms that include pain, swelling, stiffness in multiple joints, fever, and malaise.

INTRODUCTION

Arthritis, which is primarily the inflammation of joints, is one of the oldest recognized diseases affecting nearly all age demographics. In India, approximately 20% of the total population is afflicted by arthritis [1]. Rheumatoid Arthritis (RA) is a long-lasting autoimmune disorder with an unclear cause, marked by inflammation of the joint synovium and the progressive deterioration of cartilage and bone, leading to a gradual loss of mobility [2,3].

Rheumatoid arthritis (RA) is a systemic inflammatory condition characterized by progressive and irreversible damage to the joints due to chronic inflammation. Structural damage typically initiates early in the progression of the disease, and its advancement can result in diminished functional capacity. Patient-reported pain is prevalent in RA, even among individuals who have reached inflammatory remission as evaluated by standard clinical metrics; enhancements in disease activity may only explain 40% of the reported alleviation in pain [4].

Rheumatoid arthritis (RA) ranks among the most prevalent types of arthritis, exhibiting prevalence rates that range from 0.3% to 4.2%, contingent upon the specific population examined. The severe and chronic joint pain associated with RA is a debilitating symptom that is frequently highlighted as a major concern by patients. This pain typically manifests in the small joints of the hands, wrists, and feet, but it can also affect the elbows, neck, knee, shoulders, ankles or hips.

There are link between RA and other disease which related to autoimmune disease origin that common among those. There exists a correlation among the alleles associated with rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, multiple sclerosis, and ankylosing spondylitis. The origin of RA incidence regard to genetic and environmental factors. Infection represents an additional environmental factor and may provide further insight into the potential etiology of rheumatoid arthritis (RA). A leading candidate for a microbial trigger of RA is the Epstein-Barr virus (EBV).

Upon the host's attack, the initial event that takes place is the activation of CD4+ helper T-cells, which subsequently release local inflammatory mediators and cytokines. Shortly after, the endothelial cells of synovial capillaries are activated, leading to the expression of intercellular adhesion molecule-1 (ICAM-1). This process facilitates the migration and attachment of additional inflammatory cells to the impacted joint. Simultaneously, as CD4+ cells are being activated, B cells are also stimulated, resulting in the production of antibodies within the affected joints.

MATERIALS AND METHODS

This study was based on research studies indexed in Scopus, Science Direct, PubMed, and Google Scholar databases. Also, keywords used during the search include: "Rheumatoid", "Rheumatoid Arthritis Disease", "Rheumatoid, Osteoarthritis and Drugs", "Pain and Drug", "Rheumatoid Disease and NSAIDs Drugs".

RESULTS

Rheumatoid arthritis (RA) is a long-lasting autoimmune condition marked by inflammatory activities that lead to joint swelling, inflammation, and the emergence of pain. Osteoarthritis (OA) and rheumatoid arthritis (RA) lead to persistent pain, which can encompass both nociceptive and non-nociceptive elements, including neuropathic factors, as a result of peripheral inflammation and central sensitization [5].

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Both selective and nonselective cyclooxygenase (COX) inhibitors exhibit antipyretic, analgestic, and anti-inflammatory properties, and they are extensively utilized in the management of various painful conditions, including rheumatic diseases.

Both traditional NSAIDs and COX-2 inhibitors are linked to a heightened risk of cardiovascular issues [6]. NSAIDs have the potential to elevate blood pressure, especially in individuals with hypertension [7].

In contrast to certain clinical beliefs, the risk of gastrointestinal complications is evident from the initial dose of a non-selective NSAID, and the use of a proton pump inhibitor (PPI) in conjunction does not ensure total protection. COX-2 selective NSAIDs, particularly when used alongside a PPI, offer preventive measures against NSAID-induced gastropathy [8]. The frequency and intensity of gastrointestinal adverse effects related to NSAID treatment tend to rise with age, which restricts their clinical applicability in older adults, especially when used concurrently with low-dose aspirin, commonly taken by many elderly individuals for heart protection.

Paracetamol

The antipyretic and analgesic properties of paracetamol (also known as acetaminophen or APAP) have been recognized since the late 19th century.

Even when taken at the recommended therapeutic dosage of up to 4 g/d, otherwise healthy adults may display unusually elevated levels of aminotransferase. Although there exists a risk of hepatotoxicity at elevated doses, one study indicated that paracetamol significantly raised blood pressure in ambulatory patients suffering from coronary artery disease [9].

Tramadol

Tramadol is classified as a weak opioid according to the WHO pain ladder. There is a potential risk of dependence or abuse associated with tramadol; the incidence of abuse or dependence over a 12-month period has been noted in patients experiencing chronic non-cancer pain. The recommended maximum dosage should not surpass 400 mg/d and should be adjusted or closely monitored in elderly patients (≥ 75 years) and individuals with cirrhosis or renal impairment [5,10]. It is important to note that tramadol does not possess any known anti-inflammatory properties.

Opioids

Since 1990, opioids have been advocated for use in the management of long-term non-cancer pain syndromes [11]. While opioids are effective in alleviating chronic pain, they are also linked to various side effects, such as nausea, constipation, and drowsiness. The use of opioids in the elderly may be appropriate under careful supervision, often at lower dosages.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs, such as amitriptyline, dothiepin, and imipramine) function through multiple mechanisms, including the inhibition of serotonin and norepinephrine reuptake as well as the blocking of neuronal sodium channels. Their benefits include the enhancement of fatigue and sleep disorders [12]. However, TCAs are associated with certain adverse effects, including cardiac toxicity, sedation, dizziness, blurred vision, constipation, and dry mouth, which may limit their use in treatment. Dry mouth is particularly concerning for rheumatoid arthritis patients with secondary Sjögren's syndrome [5].

Anticonvulsants

Anticonvulsants, such as gabapentin and pregabalin, interact with the alpha2delta subunit of calcium channels and influence the release of neurotransmitters. Anticonvulsants, such as gabapentin and pregabalin, attach to the alpha2delta subunit of calcium channels and influence the release of neurotransmitters, which include glutamate, noradrenalin, serotonin, and substance P [5].

Serotonin Norepinephrine Reuptake Inhibitors

Serotonin norepinephrine reuptake inhibitors (SNRIs) selectively inhibit the reuptake of serotonin and/or norepinephrine, with examples including duloxetine and milnacipran. These medications may prove beneficial in managing symptoms related to sleep. A recent study indicated that duloxetine was an effective analgesic for patients suffering from osteoarthritis (OA) of the knee [13].

Corticosteroids

The long-term effects of glucocorticoid therapy can lead to complications such as glucocorticoid-induced osteoporosis and an increased risk of fractures, immunosuppression, a heightened susceptibility to infections, weight gain, thinning of the skin, muscle weakness, Cushing's syndrome, the onset of diabetes or exacerbation of pre-existing diabetes, hypertension, glaucoma, cataracts, and delayed wound healing [14,5].

Topical Agents

Topical treatments, including lidocaine, diclofenac, capsaicin, and salicylate, provide patients with localized pain relief. They are primarily utilized alongside systemic agents in the management of pain associated with rheumatic diseases. In combination regimens, topical agents may reduce the need for analgesics. Side effects are generally mild and may include skin irritations. Topical diclofenac has been shown to effectively alleviate pain resulting from OA of the knee [15].

DISCUSSION

Rheumatoid Arthritis (RA) is a long-lasting autoimmune disorder with an unclear cause, impacting 0.5% of the population. It can lead to disability due to the destruction of joints, which is marked by inflammation of the joint synovium and the progressive deterioration of cartilage and bone, ultimately resulting in a gradual loss of mobility.

Despite the association of various risk factors, including genetics, age, sex, obesity, and infections, with a heightened likelihood of developing rheumatoid arthritis (RA), the exact cause of the disease remains unidentified [16]. Recent research indicates that RA could be triggered by the interaction between susceptible genes, like HLA-DRβ1 [17], and environmental influences such as cigarette smoking [18]. For instance, the act of smoking cigarettes may lead to the expression of peptidyl arginine deiminase (PAD) by alveolar macrophages in the lungs, which facilitates the conversion of arginine into citrulline within the airway. This procedure produces a neoantigen that initiates an immune response, leading to the formation of anti-citrullinated protein antibodies [19]. Although numerous patients generate autoantibodies, not all advance to the actual disease. In certain instances, patients may evolve from autoimmunity to immune-mediated inflammation primarily localized in the synovium. The generation of these antibodies is performed by plasma cells located in the synovium. Rheumatoid arthritis (RA) is marked by the infiltration of various types of immune cells into the synovium, which includes innate immune cells (such as monocytes, dendritic cells, and mast cells) and adaptive immune cells (such as T-helper 1, Th1, T-helper 17, Th17), B cells, and plasma cells. Furthermore, synovial fibroblast-like synovial cells experience activation [20-24]. Cytokines and chemokines, including tumor necrosis factor (TNF), interleukin-6 (IL-6), and granulocyte-monocyte colony-stimulating factors, stimulate endothelial cells and attract immune cells to the synovial area [19].

The fibroblast-like synovial cells present in the synovial fluid affected by rheumatoid arthritis (RA) undergo a transformation into a more aggressive and infiltrative variant. These fibroblast-like synoviocytes, along with inflammatory cells, generate receptor activators of nuclear factor kappa-B ligand, which triggers the formation of osteoclasts, resulting in bone erosions, a hallmark of RA [21,19]. Fibroblast-like synoviocytes (FLS) migrate between joints, leading to progressive joint degeneration. Genetic mechanism and some molecules like CD4+ is important for initial inflammation process which lead to Arthritis.

CONCLUSION

To achieve effective treatment, individuals diagnosed with rheumatoid joint inflammation necessitate a blend of non-pharmacological and pharmaceutical interventions. The prevailing standard of care advocates for prompt initiation of treatment using disease-modifying anti-rheumatic drugs. Improving medical outcomes demands a holistic strategy that encompasses personal education, therapy, and physiotherapy.

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REFERENCES

1. Patwardhan SK, Bodas KS, Gundewar SS. Coping with arthritis using safer herbal options. Int J Pharm Pharm Sci. 2010; 2: 1-11.
2. Harris ED. Rheumatoid arthritis: Pathophysiology and implications for therapy. N Engl J Med. 1990; 322: 1277-1289.
3. Wadekar JB, Sawant RL, Patal UB. Rheumatoid arthritis and herbal drugs: A review. J Phytopharmacol. 2015; 4: 311-318.
4. Taylor PC, Alten R, Álvaro Gracia JM, Kaneko Y, Walls C, Quebe A, et al. Achieving pain control in early rheumatoid arthritis with baricitinib monotherapy or in combination with methotrexate versus methotrexate monotherapy. RMD Open. 2022; 8: e001994.

5. van Laar M, Pergolizzi JV Jr, Mellinghoff HU, Merchante IM, Nalamachu S, O'Brien J, et al. Pain treatment in arthritis-related pain: beyond NSAIDs. Open Rheumatol J. 2012; 6: 320-330.

6. Antman E, Bennett J, Daugherty A, Furberg C, Roberts H, Taubert K. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation. 2007; 115: 1634-1642.

7. Gaziano J. Nonnarcotic analgesics and hypertension. Am J Cardiol. 2006; 97: 10E-6E.

8. Ofman JJ, MacLean CH, Straus WL, Morton SC, Berger ML, Roth EA, et al. A metaanalysis of severe upper gastrointestinal complications of nonsteroidal antiinflammatory drugs. J Rheumatol. 2002; 29: 804-812.

9. Sudano I, Flammer AJ, Périat D, Enseleit F, Hermann M, Wolfrum M, et al. Acetaminophen increases blood pressure in patients with coronary artery disease. Circulation. 2010; 122: 1789-1796.

10. Kroenke K, Krebs E, Blair M. Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. Gen Hos Psych. 2009; 31: 206-219.

11. Trescot AM, Helm S, Hansen H, Benyamin R, Glaser SE, Adlaka R, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. Pain Phys. 2008; 11: S5-S62.

12. Perrot S, Javier R-M, Marty M, LeJeunne C, Laroche F. Is there any evidence to support the use of anti-depressants in painful rheumatological conditions? Systematic review of pharmacological and clinical studies. Rheumatology. 2008; 47: 1117-1123.

13. Chappell AS, Ossanna MJ, Liu-Seifert H, Iyengar S, Skljarevski V, Li LC, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain. 2009; 146: 253-260.

14. Franchimont D. Overview of the actions of glucocorticoids on the immune response: a good model to characterize new pathways of immunosuppression for new treatment strategies. Ann NY Acad Sci. 2004; 1024: 124-137.

15. Haynes S, Gemmell H. Topical treatments for osteoarthritis of the knee. Clin Chiroprac. 2007; 10: 126-138.

16. Deane KD, Demoruelle MK, Kelmenson LB, Kuhn KA, Norris JM, Holers VM. Genetic and environmental risk factors for rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2017; 31: 3-18.

17. Raychaudhuri S, Sandor C, Stahl EA, Freudenberg J, Lee HS, Jia X, et al. Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. Nat Genet. 2012; 44: 291-296.

18. Ishikawa Y, Terao C. The impact of cigarette smoking on risk of rheumatoid arthritis: A narrative review. Cells. 2020; 9: 475.

19. Ghazanfari M, Sepehrnia S. Reviewing Advances in Rheumatoid Arthritis Treatment: From Disease-modifying Antirheumatic Drugs to Innovative Drug Delivery Systems. Immunoregulation. 2024; 6: 105-118.

20. Fang Q, Zhou C, Nandakumar KS. Molecular and cellular pathways contributing to joint damage in rheumatoid arthritis. Mediators Inflamm. 2020; 2020: 3830212.

21. López-Mejías R, Carmona FD, Genre F, Remuzgo-Martínez S, González-Juanatey C, Corrales A, et al. Identification of a 3'-Untranslated Genetic Variant of RARB Associated With Carotid Intima-Media Thickness in Rheumatoid Arthritis: A genome-wide association study. Arthritis Rheumatol. 2019; 71: 351-360.

22. Reddy D, Trost LW, Lee T, Baluch AR, Kaye AD. Rheumatoid arthritis: Current pharmacological treatment and anesthetic considerations. Middle East J Anesthesiol. 2007; 19: 311-333.

23. Jawaheer D, Seldin MF, Amos CI, Chen WV, Shigeta R, Monteiro J, et al. A genomewide screen in multiplex rheumatoid arthritis families suggests genetic overlap with other autoimmune diseases. Am J Hum Genet. 2001; 68: 927-936.

24. COTRAN R, KUMAR V, COLLINS T. Robbins Pathologic Basis of Disease. 6th Ed. Philadelphia. 1999: 1248-1251.