A Comparative Review of Current Therapeutic Approaches and Future Prospects of Rheumatoid Arthritis

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Abstract. Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects a large number of patients worldwide, causing enormous pain and imposing significant economic burdens on both individuals and society. Although the origin of RA remains unknown, evidence suggests that both genetic and environmental factors contribute to the disease. Once initiated, RA causes inflammation in the synovial joints, eventually leading to joint deformation and bone erosion. Currently, there is no definitive cure for RA; however, years of research and technological advances have provided numerous therapeutic approaches that can improve patients' conditions. Different patients respond differently to various therapies, making it important to summarize all categories of therapeutic approaches and their prospects. This review demonstrates the complex nature of RA by analyzing its etiology and pathogenesis. It then explains the major drugs used today and their comparative advantages. Potential treatments like CAR-T cell therapy, stem cell therapy, and nanotechnology-based approaches are also discussed, along with the challenges each method faces. This paper provides a general review of RA treatment and serves as a reference for future therapeutic research. Although the specific cause of RA remains unclear, this area could be an important direction for future study and holds the potential for achieving optimal treatment.

Keywords: Rheumatoid arthritis, Therapeutic approaches, NSAIDs, Corticosteroid, DMARDs.

1. Introduction

In 2020, rheumatoid arthritis (RA) affected an estimated 17.6 million people worldwide and it is growing rapidly, one study shows that an estimated 31.7 million individuals will be living with RA in 2050 [1]. It causes severe pain and economic burden for patients and society, and it will only get worse. It is the most prevalent autoimmune disease, yet it lacks a definitive cure; current treatments mainly manage disease progression to alleviate symptoms and improve quality of life. Therefore, advances in RA treatment are in dire need. Autoimmune disease is often result from genetic factor which immune system respond to incorrectly to body [2]. In the case of RA, the abnormal immune response targets the synovial joints and initiates inflammation which leads to deformation and bone erosion eventually. Other organs lie skin, lungs, eyes, and blood vessel can also be affected [3]. Patient usually experiences stiffness of the joints, swelling, fatigue, fever, and rheumatoid nodules under the skin [4]. Other arthritis like osteoarthritis (OA) is caused by abrasion instead of immune system. OA affects different areas and has no effects on the lungs, heart, or immune system when compared with RA. In addition, OA does not have the symmetrical nature of RA [4]. Thus, RA has much infamous reputation and significant socioeconomic impact.

The burden of RA rise Dramatically with the development of novel drugs like Disease-modifying antirheumatic drugs (DMARDs), the cost for one patient is estimated up to 36000 USD annually [5]. A Medicare study claimed that the annual mean costs for RA patients were more than two times higher than those for other patients [5]. This will obviously strain the current health care system, potentially leading to a healthcare crisis as the number of patients grows. Given the severity of RA's impact on the healthcare system, it is important to evaluate the current treatment and explore prospects to ensure effective management of RA and optimize patient outcomes.

RA treatment has evolved over the years, advance in technology allows the development of new classes of medication that can improve the outcome greatly [6]. The aim is to "achieve the lowest possible level of arthritis disease activity and remission if possible, minimizing joint damage, and enhancing physical functions and quality of life" [6]. Current methods includes surgical intervention,

NSAIDs, Corticosteroids, traditional and biological DMARDs which all target different pathways. Although those treatments are able to improve the symptoms, finding the optimal treatment for RA patients will be a challenge. Additionally, RA treatment needs a comprehensive program involves not only the pharmacological approach, but also the understanding by patients and family to increase their willingness to seek medical advice, lifestyle alternation, and the diagnostic capability of the physician [5]. Thus, it is crucial to understand and combine the etiology, pathogenesis, and treatment to provide the best outcome overall. This review will summarize the pathogenesis of RA and compare the contemporary therapeutic approaches with future prospects for optimizing RA treatment.

2. Etiology and Pathophysiology

2.1. Etiology

The exact cause of rheumatoid arthritis remains unclear; however, recent evidence suggests that both genetic and epigenetic factors, along with environmental exposures—such as cigarette smoke and dust—contribute to its development [7]. Heritability, which quantifies the variation in disease susceptibility attributable to genetic factors, was estimated at 66% in a study of identical twins. This finding also implies that environmental influences, likely including infectious agents, play a crucial role [8].

Many genetic risks associated with RA have been discovered, however, most of them are not specific to RA but other autoimmune diseases as well. However, Human Leukocyte Antigen (HLA) is unique in RA as the strongest genetic predisposition with the inheritance of HLA-haplotypes. These are characterized by HLA-DRB1 alleles that specify molecules bearing shared epitope [9]. SEs will affect the antigen presentation which influence T-cell reactivity and autoantibody production. Individuals bearing these alleles will have higher susceptibility to generating anti-citrullinated protein antibodies (ACPA) and ultimately trigger RA.

Smoking stands as the most significant environmental risk factor for rheumatoid arthritis, with smokers experiencing a two-fold increase in risk compared to non-smokers [10]. In contrast, alcohol consumption appears to reduce the risk of RA. For instance, a Danish study found that individuals who drank alcohol had a lower overall risk of developing ACPA-positive RA compared to those who did not consume alcohol [11]. Additionally, factors such as obesity and high birthweight have been linked to an increased risk of RA, whereas higher vitamin D levels and fasting have been associated with reduced disease activity [10].

2.2. Pathogenesis

RA starts by changing a positively charged arginine to a polar but neutral citrulline as the result of a post-translational modification which catalyzed by peptidyl-arginine-deiminase (PAD) [5]. For those individuals who carry certain genes like HLA-DRB1, this protein will be recognized as foreign and trigger an abnormal antibody response. The antigen-presenting cell will present this protein to T cells, which will help B cells to produce ACPA. ACPA will react with citrullinated protein to form an immune complex to stimulate macrophages and dendritic cell. These immune cells will then secrete pro-inflammatory cytokines like TNF-alpha, IL-1 and IL-6 [12]. The presence of immune complexes and previous cytokines will further stimulate more T cells and B cells; therefore, it will form an inflammatory cascade. Finally, the inflammatory cytokines will activate synovial fibroblasts and lead to cartilage damage and bone erosion.

3. Current Therapeutic Methods

RA treatment has evolved into numerous varieties since researchers develop drugs targeting different pathogenesis. They can manage to relieve pain, lower activity, and slower disease progression; however, they have different effects under different scenarios, and they do have side effects. Moreover, costs must be considered not only in less affluent nations but also in countries

where medications are affordable yet the healthcare system must control spending [13]. This part of the paper will summarize the five major therapeutic approaches in treating RA.

3.1. NSAIDs

Non-steroidal Anti-Inflammatory Drugs (NSAIDs) is used extensively in RA Due to their strong anti-inflammatory and pain-relieving properties. Generally, it can relieve pain, swelling and stiffness but it does not halt disease progression.NSAIDs as a class of drugs have many different chemical structures, but they share the property of blocking the production of prostaglandins [14]. This is accomplished by inhibiting the activity of the cyclooxygenase (COX). COX has two isoforms, COX-1 will express PG under basal conditions while COX-2 expression is increased during inflammation and other pathologic situations [15]. Salicylic acids like acetylsalicylic acid (aspirin) and propionic acids like ibuprofen(advil) are classical examples of NSAIDs.

NSAIDs share a common spectrum of clinical toxicities although the frequency of side effects varies with the compound. The side effects include gastrointestinal toxicity like dyspepsia, renal toxicity like hypertension, cardiovascular toxicity like stroke, asthma and nervousness. For example, Ibuprofen is a conventional NSAIDs that can inhibit both COX-1 and COX-2, however, it will increase the risk of gastrointestinal bleeding. Celecoxib is a new NSAIDs that only target COX-2 and it has lower gastrointestinal toxicity, but it will increase the risk of cardiovascular diseases [16]. With all these side effects, patients at risk of side effects should have lowest dose of a short-acting NSAIDs for the shortest time required [16]. To summarized, NSAIDs, is best used in short-term acute pain, long-term relief require accompany with other drugs.

3.2. Corticosteroids

Corticosteroids such as prednisone have both anti-inflammatory and immunoregulatory activity. They can bind with receptors after entering the cell to form a complex. This complex will control the expression of inflammatory gene, lowering the production of the inflammatory cytokines to reduce inflammation. They can work incredibly fast and due to their rapid effect; corticosteroid have an appealing profile for treating flares or as “bridging” agents in early RA [17]. This is crucial in the early phase of RA because of the concept of a “window of opportunity” , where delaying treatment is associated with impaired outcomes [17].

However, despite their formidable rapid effect, their side effect is equally significant. They include osteoporosis, cardiovascular and metabolic effects, and increased risk of infections. Due to their adverse effect, corticosteroid can only be taken as a short-term or support treatment to achieve long term disease control.

3.3. DMARDs

Disease-modifying antirheumatic drugs are a class of drugs indicated for the treatment of inflammatory arthritis including RA. Unlike NSAIDs and corticosteroids which are symptomatic treatments, DMARDs target the immune-mediated inflammatory process. DMARDs are immunosuppressive and immunomodulatory agents that classified as conventional DMARDs and biologic DMARDs [18], this section will focus on conventional DMARDs.

Conventional DMARDs represent a diverse group of medications, each targeting specific pathways to modulate the immune response. They work by decreasing the production of inflammatory cytokines, which helps slow disease progression, though their full effects often take several months to manifest. For example, methotrexate is regarded as the cornerstone of RA treatment; it promotes the release of adenosine from fibroblasts, diminishes neutrophil adhesion, inhibits leukotriene B4 synthesis, reduces local IL-1 production, lowers IL-6 and IL-8 levels, suppresses cell-mediated immunity, and decreases synovial collagenase gene expression [18]. In contrast, leflunomide works by inhibiting dihydroorotate dehydrogenase, thereby blocking pyrimidine synthesis and lymphocyte proliferation. Sulfasalazine achieves its anti-inflammatory effects by preventing oxidative, nitrative, and nitrosative damage, while hydroxychloroquine acts as a mild

immunomodulator by inhibiting the intracellular toll-like receptor TLR9 [18]. These agents have proven effective in reducing disease activity and slowing joint damage over the long term, backed by extensive clinical experience that supports their safety profile. Although conventional DMARDs can be more costly than NSAIDs and corticosteroids, they are generally less expensive than the newer biologic treatments.

Another notable feature of DMARDs is the need for constant monitoring. For conventional DMARDs like methotrexate, it need regular monitoring of liver enzymes, renal function, and complete blood count due to the risk of hepatotoxicity, bone marrow suppression, and renal impairment. Other medicine's needs may vary but it is a crucial step for early detection of adverse events and ensuring ongoing efficacy.

3.4. Biologic DMARDs

Biologic DMARDs are proteins like monoclonal antibodies that target specifically in immune system. It was introduced in 1990s and are usually prescribed after the failure of conventional DMARDs therapy [18]. One important advantage they have than conventional DMARDs are that they are designed to interfere with precise molecule rather than a broad immunosuppressive effect. Agents include infliximab, adalimumab, etanercept, rituximab, abatacept, rituximab, tocilizumab, tofacitinib are all biological DMARDs [18]. They then can be classified with different inhibition. TNF inhibitors is a major branch of the bio-DMARDs, Adalimumab is a classical IgG which target TNF-alpha. TNF-alpha is the key cytokine in RA as it can binds to TNF receptors on immune cells, triggering an inflammatory signaling cascade. Adalimumab will recognize and attach to the same binding region that TNF-alpha used to interact with TNF receptors, therefore, blocking it binding and effectively stop the inflammatory signaling cascade [19]. Another example is Rituximab, which is a B-cell depleting agent. It will targets CD20 on B-cells and leading to their depletion and reduce the autoantibody production and antigen presentation. It is often used when patients with an inadequate response to TNF inhibitor like adalimumab. It is now the most popular treatment and various studies on it targeting different protein are in progress as demonstrated in table 1.

Bio-DMARDs do not come without adverse effect. As is suppressing the specific parts of the immune system, it also reduces individual's ability to fight infections. When considering bacterial infections, tuberculosis and hepatitis. It is also much more expansive than conventional DMARDs, therefore, it will become a significant economic burden on individuals and healthcare systems.

Biological DMARDs also need monitoring [20]. Other ongoing monitoring like liver enzyme is also important to ensure the safety of patient.

Table 1. Some biologic DMARDs and their development statues

Agent	Target protein	Status
Adalimumab	TNF	Market
Tocilizumab	IL-6R	Market
Canakinumab	IL-1	Market
BX147	CCR1	Animal study
AMG-714	IL-15	Phase 2
ABN912	CCL2	Phase 1
Secukinumab	IL-17	Phase 3

3.5. Targeted synthetic DMARDs

Targeted synthetic DMARDs are a newer class of DMARDs, they are typically chemically synthesized, smaller compounds rather than proteins in the case of biologic DMARDs. They are usually easier to produce since they don't need to use complex synthetic biology, therefore the cost of tsDMARDs will be lower. They also have a different mechanism of action, tsDMARDs inhibit specific intracellular enzymes or signaling molecule, while biological agent targets extracellular

proteins such as cytokines. By targeting specific pathways inside the cell, tsDMARDs can disrupt the downstream effects of multiple cytokines simultaneously.

JAK inhibitors are a prime example of targeted synthetic DMARDs. The JAK-STAT signaling pathway plays a key role in rheumatoid arthritis by promoting inflammation [3]. Cytokines such as IL-6, IL-7, IL-12, and IL-15 bind to type I/II cytokine receptors, triggering downstream signaling that leads to inflammatory events. Tofacitinib, an oral JAK inhibitor, targets multiple JAK isoforms—primarily JAK1 and JAK3 [3]. By inhibiting the activity of these enzymes, it disrupts cytokine signaling and consequently halts the inflammatory cascade.

The side effect of tsDMARDs is similar to biologic DMARDs, it inhibits the immune signaling and decreases individual's ability to stop infections. It requires constant monitoring for any adverse effects like gastrointestinal toxicity.

4. Emerging Therapies

Although last section illustrates some promising therapeutic approaches to RA treatment, it does not stop researchers from pushing the limit of drug development. Especially, many patients respond differently to various methods. There are several promising novel therapeutic approaches for RA that show exciting feedback and are currently being studied. They are developed to improve efficacy, reduce side effects, and ultimately find the optimal treatment. Below are novel treatment and potential targets that scientist believe they will have a future use.

4.1. Vagus Nerve Stimulation

The vagus nerve is a mixed nerve, comprising approximately 20% efferent and 80% afferent fibers, and acts as a two-way communication link between the brain and the body [21]. Koopman's work has demonstrated that activating the inflammatory reflex using an implantable VNS device can regulate TNF and other cytokine levels [22]. TNF is the main target for many biologic DMARDs in section 3.4. Koopman collected data from 18 patients with RA who receive VNS for 60 seconds up to four times daily. The result was collected on day 42 with lower level of TNF. However, after VNS was stopped, the TNF levels increased. This suggests withdrawal of treatment may worsen disease.

This method is still in early stage, extensive study on safety and efficacy is in progress. The VNS method will provide hope for patients who have failed to respond to biologic agents and other DMARDs.

4.2. CAR-T Therapy

Chimeric Antigen Receptor (CAR) T-cell therapy is a now breakthrough in treating cancer, and it works against lupus which is another rheumatologic condition. It is routinely used to treat B-cell malignancies and has become a groundbreaking strategy for managing severe autoimmune diseases, particularly systemic lupus erythematosus [23]. Its function and pathway for targeting B lymphocytes in autoimmune disease have been extensively studied and tested for several years and have been proven effective.

T cells are crucial part of the immune system in human body to maintain health. T cells are originally from thymus and generate CD4 and CD8 subsets, and they will differentiate into those subsets to mediating direct killing, diverse immune regulatory function, and long-term protection upon antigen stimulation [24]. In CAR-T therapy, a person's own T-cells will be removed from the body and engineered in the lab to target specific cells. This technique is widely used in cancer treatment; however, it lacks experiments and evidence to be proven effective in RA treatment. This is because RA is not life-threatening disease, and it is relatively new. The research will get to RA anyway, as it has the potential. An engineered T-cell is capable of eliminating the excess protein and other immune cells contributing to RA. The case of Lupus is an example and a starting point for RA research.

4.3. Stem Cell Therapy

Mesenchymal stem cell (MSC) therapy has demonstrated potential in preclinical studies for reducing inflammation and enhancing tissue repair [25]. MSCs are a type of stem cell capable of differentiating into various cell types, including B cells, T cells, and macrophages. That is why it is a powerful tool since it can cover many parts of the RA inflammation process. Evidence has shown that MSCs can mediate powerful immunoregulatory effects by inducing factors like prostaglandin, TGF-beta, and IL-10. It can also induce the macrophage from M1into M2 phenotype, as well as reduce proinflammatory T helper cells and increase the regulatory T cells of RA patients [25]. Additionally, it has the potential to treat RA by modulating the immune response the reducing inflammation. In clinical use, the stem cells can be injected into damaged tissue to lower inflammation and super charge the repair process.

As a new technology, its safety and efficacy need further investigation. Stem cell extraction, storage, administration method requires more trials before people fully utilize its power.

4.4. Nanotechnology

Nanotechnology offers a novel approach for delivering DMARDs by helping to target specific cells. Its role has become increasingly important as treatment strategies in RA shift from monotherapy to combination therapy. Nanotechnology provides an unparalleled opportunity to develop advanced combination treatments by co-delivering multiple drugs with enhanced physicochemical properties and controlled release profiles. It also enables the integration of multifunctional nanomedicines, paving the way for all-in-one nanoplatforms that incorporate various modalities, including phototherapy, sonodynamic therapy, and imaging [26]. The study on nanotechnology in RA require a joint venture from expertise across fields and it is in early stage.

4.5. Noncoding RNAs

Non-coding RNAs have three variance, microRNAs, long noncoding RNAs, and circular RNAs. MicroRNAs are short noncoding endogenous RNAs found in plasma and urine. Researchers have proven there is an association between the dysregulated miRNA expression and RA pathophysiology [3]. Especially, miRNA-146A is upregulated in the synovial fluid of RA, and miRNA-155 is upregulated in macrophages [3]. Long noncoding RNAs and circular RNAs are similar to miRNAs, all are found either upregulate or downregulate in various tissue like plasma, synovial tissues, and peripheral blood mononuclear cells. These actions will promote the expression of inflammatory cytokine and start inflammation signalling like NF-kB, IL-10, and many more. Overall, the non-coding RNAs have a significant role in the progression of RA, they will be a good target in therapeutic treatment.

Most studies on noncoding RNA are still in vitro phase. For example, miRNA-15 is a downregulation found in fibroblast-like synoviocytes-exos and it will trigger the SOX5 axis signal. It is still an in vitro phase study and it function as a key driver of RA-FLSs invasion, migration and inflammatory response in a mutual negative feedback loop and is correlated with DMRADs treatment response in RA [27].

5. Challenges

Although the treatment of RA has made significant progress as demonstrated in last two sections, the complex nature of RA is still challenging for current therapeutic approaches and new strategies. This includes the balance between safety and efficacy, contradiction between cost and accessibility, complexity of every individual patient, family and society understanding and support.

Take safety for example, DMARDs have been proven effective against RA, as they can target specific proteins in the immune system and slow disease progression. But, as mentioned before, it is a double-edged sword. The immune system is inhibited which increases the risk of infection. Traditional drugs like corticosteroids can act very fast and relieve pain, but the adverse effects can be

terrible including osteoporosis, cardiovascular and metabolic effects. Emerging therapy will have even more concern about safety, CAR-T shows promising potential for treatment, but it can trigger cytokines release syndrome, also known as cytokine storm [23]. Thus, it is always a dilemma for safety and efficacy, optimal solutions need to consider patients' conditions.

Price is also an important aspect of RA treatment, as mentioned in introduction, DMARDs could cost 36000 USD per year. This will exclude many patients from underdevelopment regions, and since DMARDs can slow disease progression rather than simply relieve pain, it could cause higher disability rate in people who cannot afford DMARDs. The good news is there are many more biosimilars been proven by governments to increase accessibility of treatment. Etanercept-szze (Erelzi) is a biosimilar form of etanercept (Enbrel) which can inhibit both TNF-alpha and TNF-beta. The biosimilars are expected to have the lower cost but similar effect to the original drug.

Another factor that cannot be ignored is the complexity of individualized treatment. Most research above states that some methods are given if the patient responds inadequately to the previous methods. For instance, treatment responses differ between ACPA-positive and ACPA-negative patients. ACPA-positive individuals receiving triple therapy derived the most benefit, whereas ACPA-negative patients showed minimal radiological progression regardless of the treatment. Additionally, corticosteroids only improved DAS28 scores in ACPA-positive RA cases [28].

Long-term monitoring is also necessary for all RA treatment. The recurrence rate is high in many therapeutic methods, a continuing monitoring allows for selection of optimal solutions. The side effects of drug are also worth notice as they increase the risk of infections.

Lastly, ethical and regulation barriers can also be challenge in RA treatment. As new technology emerges, there are signs of misuse of stem cell therapy. Many institutes are suspected of exaggerating their effect in their commercial advertisement. CAR-T therapy on the other hand, is questioned on overtreatment. It requires so many medical resources that could be used to save lives rather than treating non-fatal diseases like RA.

6. Conclusion

RA is a chronic autoimmune disease that will have patients' number up to 31 million in 2025. The treatment has also made significant progress, current methods like DMARDs can notably slow RA progression and improve quality of life, others like NSAIDs are capable of fast pain relief. However, due to the complex nature of RA pathogenesis, heterogeneity of patients, long-term optimal management of disease still needs to be resolved. This review demonstrates the etiology, pathogenesis, current treatment progress, and emerging potential technology.

Emerging treatments like CAR-T and nanotechnology have shown promising future but require further validation for safety and efficacy. The key directions for future research are interdisciplinary collaboration, cost optimization, long-term monitoring, and framework construction for law and ethic. It is a clear trend that the treatment of RA has moved from symptom control to cure. Through the deep integration of basic research and clinical practice, as well as global collaboration in policy support and resource allocation, the efficient, safe, and affordable RA treatment can be achieved.

References

[1] Black R.J. et al. Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology, 2023, 5(10): e594-e610.

[2] Pisetsky D.S. Pathogenesis of autoimmune disease. Nat Rev Nephrol, 2023, 19: 509–524.

[3] Khokhar M., Dey S., Tomo S., Jaremko M., Emwas A., Pandey R.K. Unveiling Novel Drug Targets and Emerging Therapies for Rheumatoid Arthritis: A comprehensive Review. ACS Pharmacology & Translational Science, 2024, 7(6): 1664-1693.

[4] Bullock J., Rizvi S.A.A., Saleh A.M., Ahmed S.S., Do D.P., Ansari R.A., Ahmed J. Rheumatoid Arthritis: A Brief Overview of the Treatment. Med Princ Pract, 2018, 27(6): 501-507.

[5] Guo Q., Wang Y., Xu D. et al. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res, 2018, 6: 15.

[6] Johns Hopkins Arthritis Center. Rheumatoid arthritis treatment. Johns Hopkins Medicine.

[7] Scherer H.U., Häupl T., Burmester G.R. The etiology of rheumatoid arthritis. Journal of Autoimmunity, 2020, 110: 102400.

[8] Woude V.D., Houwing-Duistermaat J.J., Toes R.E., Thomson T.W., Worthington J. Quantitative heritability of anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis. Arthritis Rheum, 2009, 60: 916-923.

[9] Hammer J., Gallazzi F., Bono E., Karr R.W., Guenot J., Valsasnini P. et al. Peptide binding specificity of HLA-DR4 molecules: correlation with rheumatoid arthritis association. J Exp Med, 1995, 181: 1847-1855.

[10] Katherine P.L., Lars A., Elizabeth W.K. Environmental influences on risk for rheumatoid arthritis. Current Opinion in Rheumatology, 2009, 21(3): 279-283.

[11] Rantapaa-Dahlqvist S., de Jong B.A., Berglin E. et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum, 2003, 48: 2741–2749.

[12] Woude V.D. Epitope spreading of the anti-citrullinated protein antibody response occurs before disease onset and is associated with the disease course of early arthritis. Ann Rheum Dis, 2010, 69: 1554–1561.

[13] Smolen J.S. EULAR recommendations for the management of rheumatoid arthritis. Annals of the Rheumatic Diseases, 2023, 82(1): 3-18.

[14] Crofford L. In: Kelley's Textbook of Rheumatology (2013). Prostanoid biology and its therapeutic targeting; pp. 871–893.

[15] Crofford L.J., Lipsky P.E., Brooks P., Abramson S.B., Simon L.S., van de Putte L.B.A. Basic biology and clinical application of specific COX-2 inhibitors. Arthritis Rheum, 2000, 15: 4–13.

[16] Crofford L.J. Use of NSAIDs in treating patients with arthritis, National Library of Medicine, July 24, 2013;15(suppl 3): S2.

[17] Doumen M., Pazmino S., Bertrand D., Westhovens R., Verschueren P. Glucocorticoids in rheumatoid arthritis: Balancing benefits and harm by leveraging the therapeutic window of opportunity. Joint Bone Spine, 2023, Volume 90, Issue 3: 105491.

[18] Benjamin O., Goyal A., Lappin S.L. Disease-Modifying Antirheumatic Drugs (DMARD) [Updated July 3, 2023]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; January, 2025.

[19] Idriss H.T., Naismith J.H. TNF alpha and the TNF receptor superfamily: structure-function relationship(s). Microsc Res Tech, August 1, 2000; 50(3): 184-95.

[20] Oo W.M., Yu S.P., Daniel M.S., Hunter D.J. Disease-modifying drugs in osteoarthritis: current understanding and future therapeutics. Expert Opin Emerg Drugs, December, 2018; 23(4): 331-347.

[21] Foley J.O., DuBois F.S Quantitative studies of the vagus nerve in the cat: I.The ratio of sensory to motor fibers. J Nerv Ment Dis,1937;86:587.

[22] Goggins E., Mitani S., Tanaka S Clinical perspective on vagus nerve stimulation: present and future. Clin Sci(Loud), May10,2022; 136(9): 695-709.

[23] Guffroy A., Jacquel L., Guffroy B., Martin T.CAR-T cells for treating systemic lupus erythematosus: A promising emerging therapy. Joint Bone Spine, 2024; 91(5): 105702.

[24] Sun L., Su Y., Jiao A.et al.T cells in health and disease. Sig Transduct Target Ther, 2023; 8: 235.

[25] Zhang C., Ma P., Qin A.et al. Current Immunotherapy Strategies for Rheumatoid Arthritis: The Immunoengineering and Delivery Systems.Research,2023;6:0220.

[26] Ren S., Xu Y., Dong X.et al. Nanotechnology-empowered combination therapy for rheumatoid arthritis: principles, strategies, and challenges. J Nanobiotechnol, 2024; 22: 431.

[27] Wei H, Wu Q, Shi Y.et al. MicroRNA-15a/16/SOX5 axis promotes migration, invasion and inflammatory response in rheumatoid arthritis fibroblast-like synoviocytes. Aging (Albany NY), July17, 2020; 12: 14376-14390.

[28] Seegobin S.D., Ma M.H., Dahanayake C.et al. ACPA-positive and ACPA-negative rheumatoid arthritis differ in their requirements for combination DMARDs and corticosteroids: secondary analysis of a randomized controlled trial. Arthritis Res Ther, 2014; 16: R13.