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Review

Analysis of the prospects of new therapeutic agents for the treatment of rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA), a chronic autoimmune disease, is one of the major research themes in medicine. The current therapies have their limitations and cannot completely cure RA, but new therapeutic strategies are being proposed to reduce the shortcomings of approved drugs. This review will consider new potential treatment strategies for RA, including T-cell therapy, genetic editing and epigenetic regulation, what advantages and disadvantages they have and to what pathological target in RA they are directed.

Keywords: Rheumatoid arthritis, Inflammation, Gene therapy, T-cells.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation. Expressed as a systemic autoimmune illness linked to a persistent inflammatory process, RA can harm extra-articular organs such as the heart, kidney, lung, digestive tract, eyes, skin, and nervous system in addition to joints [1]. This leads to pain, swelling, and limited mobility, which significantly reduces the patient's quality of life. According to statistical data RA affects approximately 0. 5-1% of the world's population, with women suffering from this disease three times more frequently than men [2]. Quantitative data interpretation and current statistical analysis demonstrate that RA is a public health concern in addition to a medical condition. So RA is the most frequent medical cause of mobility-related functioning loss in adults in the United States [3]. Additionally, a number of health economic studies have quantified the financial impact of RA and, as a result, have shown that treating early episodes of RA or lowering risk factors will result in far cheaper costs than hospitalization and surgery [4].

Corticosteroids, disease-modifying anti-rheumatic medicines (DMARDs), and non-steroidal anti-inflammatory drugs (NSAIDs) are the three main drug classes frequently used to treat rheumatoid arthritis [5]. While DMARDs can take several weeks to demonstrate a clinical effect, NSAIDs and corticosteroids work quickly [5]. However, NSAIDs and corticosteroids are used as a quick fix for inflammation and pain and cannot affect the development of arthritis, nor can they be used long-term due to serious side effects [5]. DMARDs are the main drugs for long-term treatment of RA and can alleviate the course of the

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disease, but their action also may be connected with the development of side effects and don't lead to a full cure of RA [6].

In view of the growing cost problem of RA treatment and the shortcomings of existing approved therapeutic agents, there is a need to develop new and improved therapeutic agents for the treatment of RA that will have a better safety and efficacy profile. The purpose of this review is to systematize information about the most promising developments in the treatment of RA and compare them with existing registered drugs according to main pharmacological parameters.

2. The key stages of the rheumatoid arthritis pathogenesis

Based on the existence or lack of anti-citrullinated protein antibodies (ACPAs), there are two main subgroups of RA. The calcium-dependent enzyme peptidyl-arginine-deiminase (PAD) catalyzes the post-translational change known as citrullination, which converts positively charged arginine into a polar but neutral citrulline. About 67% of RA people with acute have ACPAs, which can be found in their disease. For undifferentiated arthritis, ACPAs can be a helpful diagnostic tool, since they can indicate the likelihood of the disease progressing to RA [7]. When compared to the ACPA-negative subset of RA, the ACPA-positive subset exhibits a more severe clinical profile.

2. 1. Initiating stage

In RA, the environment serves as a trigger for the production of ACPA, and genes and the environment are combined through epigenetic regulation. In RA, the reactivity of autoantibodies to citrullinated antigens is influenced by gene-environment interaction. It is possible to identify 2ACPAs well in advance of the joint symptoms manifesting [8]. This phenomenon raises the possibility that the joints are not the site of autoimmunity onset.

ACPA-positive RA is most strongly connected with a genetic risk factor called "shared epitopes," or genes encoding HLA-DR, particularly HLA-DR1 and HLA-DR4. It is believed that SE is a major risk factor for ACPA production since it affects RA outcomes through ACPA production [9]. The lymphoid-specific protein tyrosine phosphatase known as protein tyrosine phosphatase non-receptor type 22 (PTPN22) has also garnered a lot of attention due to polymorphisms linked to ACPA-positive RA and its role in the development of ACPA-positive RA in a variety of ethnic groups [10]. As a result, it might function as a strong antagonist of T cell activation, which would impact the synthesis of ACPA.

External risk factors for the development of RA include smoking and infectious diseases. In addition to antigen-presenting cells (APCs) like B cells and conventional dendritic cells (DCs), lung exposure to noxious chemicals such as smoke, silica dust, nanosized silica, or carbon-derived nanoparticles can activate mucosal toll-like receptors (TLRs), which in turn activate Ca2+-mediated PADs [11]. Mutations in the coatomer subunit α gene may impair the transport of endoplasmic reticulum (ER) to the Golgi apparatus, leading to autoimmune-mediated lung disorders and arthritis in hereditary cases. This suggests a link between lung and joint diseases [12]. Three infectious agents: *Porphyromonas gingivalis*, Aggregatibacter actinomycetemcomitans (Aa), and Epstein-Barr virus (EBV)—are well-supported by data as autoimmune triggers in RA. Compared to 11% of the control group, 47% of RA patients in a clinic environment had evidence of a prior Aa infection [13]. Leukotoxin A can be secreted by pathogen Aa, and it can also create holes in neutrophil membranes that cause hyper-citrullinated neutrophils, which in turn releases citrullinated autoantigens into the gums. Two mechanisms have been reported by researchers to explain how *P. gingivalis* infection causes citrullinated autoantigens and ACPA production: the first involves the action of P. gingivalis's arginine ginpains (Rgps) and PAD, which can hydrolyse proteins at arginine residues and citrullinate proteins to produce additional neoantigens [14]; the second involves the creation of neutrophil extracellular traps (NETs) during the process of NETosis. Citrullinated autoantigens are produced by NETosis, which is induced by ACPAs [15]. EBV can impact B cells that produce ACPA, and RA patients may exhibit decreased EBV control [16].

2. 2. Inflammation development

The term "epitope spreading" describes how the release of self-antigens triggers the advancement of immune responses to endogenous epitopes. The immune system's reaction to autoantigens may be present outside of the joints for many years before the disease manifests. It seems that initial ACPA levels play a major role in forecasting the time gap until the development of the disease. The breakdown of immunological tolerance is reflected in the generation of ACPA [17]. Numerous citrullination neoantigens would therefore stimulate T cells that are dependent on MHC class II, which would then assist B cells in producing more ACPA.

Leukocytes infiltrate the synovial compartment, and pro-inflammatory mediators fill the synovial fluid. These factors combine to create an inflammatory cascade, which is typified by the interactions between fibroblast-like synoviocytes (FLSs) and innate immune system cells such as monocytes, macrophages, mast cells, DCs, and so forth, as well as adaptive immune system cells like T lymphocytes and B lymphocytes. A failed attempt to resolve inflammation (chronic synovitis) is the outcome of the development of ACPA-positive RA, which is closely linked to the autoimmune interaction of these two immune systems.

It has been discovered that macrophages profoundly penetrate synovial membranes and play a key role in the pathogenesis of inflammation. NF-kB activity and TNF-α production in monocytes and macrophages can be enhanced by ACPA through its adhesion to surface-expressed citrullinated Grp78. 5 [18]. According to the study [18], patients with RA, particularly those with ACPA-positive RA, had osteoclastogenesis as a result of an imbalance in M1/M2 monocytes. Furthermore, one study found that the pro-inflammatory cytokine interleukin (IL)-17A in RA joint samples is mainly confined to mast cells, and that TLR ligand and ACPA can activate mast cells [18]. There have also been reports of DC buildup in the articular cavity [19]. CD4 effector T cells play a crucial role in aberrant immunity in RA by maintaining autoantibody synthesis and chronic synovitis. Additionally, a deficiency of reactive oxygen species may increase pro-inflammatory T cells, highlighting the significance of energy metabolism in RA [20]. B cells in RA are responsible for the antigen presentation, production and release of antibodies, and re-

lease of cytokines into the inflammation environment [21].

2. 3. Tissue degradation

Specialized FLSs and macrophages generated from bone marrow coexist in the synovium [22]. Hyaluronic acid and lubricin, which are secreted by synovial cells for joint lubrication and function, as well as waste product processing, help to maintain the stable condition of the joint. Hyperplastic synovium in RA is caused by FLS dysfunction. A loss of contact inhibition leads to the aberrant proliferation of FLS, which is a major cause of RA. This loss of inhibition produces inflammatory cytokines and proteinases, including matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), which further degrade joints. They produce a milieu that promotes neutrophil accumulation, and T-cell and B-cell survival [23].

Synovial joints depend heavily on cartilage, which is made up of chondrocytes and a dense, well-organized extracellular matrix (ECM) that these chondrocytes synthesize and that comprises type II collagen and glycosaminoglycans (GAGs). In RA, the hyperplastic synovium directs adhesion and invasion, which seriously damages the cartilage. On the other hand, inflammatory cues, such as those found in the extracellular matrix, have the ability to increase FLS activity. As a result, chondrocytes experience apoptosis and the cartilage gradually loses them due to the action of reactive nitrogen intermediates and synovial cytokines, specifically IL-1 and IL-17A [24].

One of the pathological characteristics of RA is bone loss, which can be systemic, periarticular, or localized. The activation of osteoclasts and the inhibition of osteoblasts lead to bone loss. In the context of inflammation, tumor necrosis factor-alpha (TNF-α), IL-6, IL-1β, IL-17, and other inflammatory cytokines implicated in RA may have pro-osteoclastogenic actions, inhibit bone production, and encourage the infiltration and differentiation of monocytes into osteoclasts [25].

3. Disadvantages of current rheumatoid arthritis therapy

The ultimate goal of treatment for individuals with RA is to achieve remission, or at least reduce disease activity, for every patient. Treatment targets include pain relief and inflammatory control. Unfortunately, despite the significant progress in the treatment of RA that has been achieved through approved medications, existing therapy has its limitations and disadvantages.

Combinations of synthetic disease-modifying antirheumatic medications (DMARDs) may lead to increased rates of treatment cessation and side effects. Methotrexate (MTX) ineffectiveness would be expressed more likely in individuals with higher baseline disease activity and patients with positive rheumatoid factor (RF) [26]. In certain situations, methotrexate use may result in hepatic fibrosis, which may be caused by a decrease in the liver's stores of folate and a buildup of polyglutamated methotrexate [27]. Pregnancy-related MTX exposure can result in a variety of congenital abnormalities. Therefore, it is not advised to use MTX therapy while pregnant [28].

Sulfasalazine adverse reactions are prevalent and include idiosyncratic (such as hypersensitivity/immune-related) and dose-related impacts. The gastrointestinal tract, central nervous system, cutaneous, and hematologic adverse effects are particularly common. About 25% of withdrawals are caused by adverse events, with gastrointestinal and central nervous system toxicity accounting for two-thirds of these cases. Treatment can be stopped for a week if side effects related to dosage develop, and it can be resumed at a lower dose once the symptoms have subsided. However, the treatment must be stopped right once if idiosyncratic side effects such as skin rashes, hepatitis, pneumonitis, or hematologic side effects including agranulocytosis and hemolytic anemia appear. Patients who experience these kinds of side effects shouldn't take the medication again [28]. In addition, taking sulfasalazine is associated with a risk of serious side effects such as infectious diseases (including sepsis), life-threatening systemic hypersensitivity reactions, and severe skin reactions such as toxic epidermal necrolysis [29].

The EULAR guidelines state that if a patient does not respond effectively to MTX and/or other csDMARD treatments if unfavorable prognostic markers (such as high acute phase reactant levels, high swollen joint counts, or the appearance of early erosions) present, or if remission or LDA is not obtained with the first DMARD therapy, a biological DMARD should be considered for the treatment but their use also may be associated with the cirtain limitation. When taking monoclonal antibodies against TNF-α, delayed infusion events can also happen. These reactions are linked to skin rashes, myalgia, widespread joint pain, and exhaustion. Fever is occasionally also present. Mild type III (immune complex-mediated) reactions may be represented by delayed reactions. Research has demonstrated that the development of anti-monoclonal antibodies may increase the risk of infusion responses and may also reduce the medication's long-term effectiveness [30]. The disadvantages of the current RA therapy are grouped in Table 1.

4. New therapeutic strategies for the treatment of rheumatoid arthritis

The development of new treatment options for rheumatoid arthritis can not only mitigate the shortcomings of current RA therapy but also contribute to the discovery of new therapeutic targets, which will allow us to take a different look at the pathogenesis of RA in general.

4. 1. Cell therapy

In the context of RA, the idea of using cell-based the-

Table 1. The disadvantages of the current RA therapy.

Drug	Possible negative effect	Group of patients
methotrexate	hepatic fibrosis	patients with positive RF
	congenital abnormalities of fetus	pregnant women
sulfasalazine	gastrointestinal and CNS toxicity, sepsis, severe skin reactions	Different RA patients
monoclonal antibodies	delayed infusion events, development of anti-monoclonal antibodies	Different RA patients

rapy involves modifying or adjusting immune cells to restore immunological homeostasis. Mesenchymal stem cell (MSC) therapy has shown promising results in early-phase clinical studies because it efficiently controls the inflammatory response and promotes tissue healing (NCT01851070). Chimeric antigen receptor T-cell (CAR-T) treatment is an additional tactic that targets autoreactive immune cells. Comparable to how CAR T cell therapy treats cancer, it targets autoantigenic B cells, which trigger autoimmune reactions, without impacting the immune system as a whole in autoimmune diseases. The CAR molecules consist of an intracellular domain derived from T cell receptor (TCR) signaling proteins and an extracellular domain made up of a single chain variable segment of an antibody that confers specificity for the particular targeted cell antigen [31]. While more research is still required, researchers are currently working on creating a universal CAR-T therapy that can recognize and target autoreactive cells using key epitope peptides [31]. It has been demonstrated that CAR T cells that selectively target CD19 can cause complete B cell aplasia with a single infusion, maintain humoral immunity that was already present, and eradicate pathogenic B cells. Its capacity to produce a targeted and durable remission makes it a viable treatment strategy for autoimmune disorders [32].

But like other SRDs, CAR T cell therapy for RA is limited in that it only targets a single cell type, which makes it unsuitable for treating the diverse population of autoreactive lymphocytes that RA patients have [31]. In order to get over this restriction, it had been conducted a proof of concept investigation using FITC-labeled RA-immunodominant peptides in combination with universal anti-fluorescein isothiocyanate (FITC) CAR T cells [33]. This study demonstrated that, depending on the availability of the pertinent FITC-labeled antigenic peptides, numerous strains of hybridoma cells can be targeted and killed by the anti-FITC CAR T cells via lysis, providing a solution for the varied nature of RA treatment with CAR T cells. By targeting distinct autoreactive B cell subsets, this strategy attempted to give RA patients a more targeted and long-lasting therapeutic alternative.

In the other research, a method of treating autoimmune disorders was employed that specifically targets the pathogenic CD4+ T cells that cause the pathology of the disease by integrating a model autoantigen and HLA-DRB1×01:01 (DR1) into the CAR molecular structure [34]. The resultant DR1 CAR T cells solely target cells expressing a TCR confined to DR1 and specific for the antigenic peptide, lysing CD4+ T cells in an antigen-specific manner. Both the B cell autoantibody reaction and the severity of RA were lessened by the DR1 CAR T cells.

One subset of immune cell known as natural killer (NK) cells is capable of identifying and eliminating aberrant cells, such as cancerous and infectious cells. NK cells have been shown to operate poorly in RA. Ex vivo-expanded NK cell infusion was found to be safe and to lower disease activity in patients with RA in a clinical investigation [35].

4. 2. Gene reduction

The field of RA treatment now has intriguing new potential factors for the development of gene editing technology. It is possible to precisely modify genes linked to disease using the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 technology, which may have long-lasting therapeutic effects [36]. Research has indicated that cytokines from the IL-36 family may be crucial in the emergence of autoimmune disorders, such as RA [37]. It is well known that IL-36 stimulation activates the adaptor protein known as myeloid differentiation primary response gene 88 (MyD88). The activity of differentially expressed genes that induce the production of IL-1B and IL-36G was decreased by the CRISPR-Cas9-mediated inactivation of the MyD88 adaptor protein [38]. It has been observed that the genetic variant of TNFAIP3 is linked to an increased risk of developing RA [39]. According to a study on TNFAIP3 knockout mediated by transcription activation-like effector nuclease (TALEN), autoimmune symptoms associated with pathogenic TNFAIP3 variations may be reversed by correcting the variant [40]. Furthermore, the CRISPR-Cas9 gene editing method that knocked out a putative causative mutation, rs6927172, affected the expression of the TNFAIP3 and IL-20RA genes, which may be implicated in the autoimmune response [40].

Rheumatoid arthritis has been linked to the MYC and FOXO1 genes, according to certain hypotheses [41]. It was previously described that MYC regulated the autophagy pathway and that CD4+ T-cells expressed increased levels of autophagy in RA patients [41]. There is also a theory that FOXO1 and RA activity are connected [41]. This research offers evidence that MYC and FOXO1 genes may be causative factors of RA by gathering ATAC-seq, Hi-C, Capture Hi-C, and nuclear RNA-seq data in activated CD4+ T cells during 24 hours [41]. A genome-wide association conducted research revealed that an intergenic SNP, rs6927172, on the chromosome 6q23 area, was linked to the course of the RA disease [42]. The study found that several genes, including TNFAIP3, OLIG3, IFNGR1, IL20RA, and IL22RA2, flank the SNP region [42]. When the SNP area was disrupted using CRISPR-Cas9, only TNFAIP3 and OLIG3 had lower expression [42]. It demonstrates that TNFAIP3, OLIG3, and SNP rs6927172 are significantly linked to the progression of RA illness. MicroRNA 155 (miR-155) has been shown to be a potential pro-inflammatory factor in patients with RA. Using an RAW 264. 7 macrophage cell line with miR-155 deletion, it was discovered that SHP1 was upregulated and the cell line's ability to produce pro-inflammatory cytokines was compromised [43]. As a result, it has been proposed that miR-155 genome editing may be a useful RA treatment approach.

4. 3. Epigenetic regulation

Histone alterations may play a role in the onset and progression of RA, according to recent studies. Changes to histones can have an impact on gene expression and protein synthesis. Histones are proteins that aid in the packaging and organization of DNA in the nucleus of cells. There are several ways to alter histones, including phosphorylation, acetylation, methylation, and poly ADP-ribosylation. It was discovered that in PDGF-induced FLS, the Akt signaling pathway elevated the expression of Jumonji C family of histone demethylases (JMJD3). JMJD3 inhibition or silence decreased FLS's ability to proliferate and migrate, and it also relieved the symptoms of collagen-induced arthritis (CIA) in DBA/1 mice [44]. Simultaneously, it has been discovered that CSE/H2S can alleviate arthritis and block transcription factor Sp-1, hence reducing the

expression of JMJD3 [45]. GATA4 regulates heart function in a significant way. It was found that GATA4 was up-regulated in MH7A triggered by IL-1β and that it may control blood vessel formation through the MAPK signaling pathway as well as the proliferation and migration of endothelial cells. It might provide beneficial suggestions for RA treatment. Histone deacetylases (HDACs) may play a role in the onset and development of RA, according to recent studies. Research has demonstrated that RA patients' synovial tissues have higher levels of HDACs and that blocking HDACs can lessen inflammatory reactions [46]. HDAC1 plays a major role in arthritis that is T cell-mediated [47]. HDAC inhibitors have been demonstrated to enhance the activity of regulatory T cells and lower the synthesis of pro-inflammatory cytokines including TNF-α and IL-6, which may aid in the suppression of the immunological response in RA [48]. Pre-clinical research is presently being conducted on a number of HDAC inhibitors as possible RA therapies, including HDAC6 inhibitors CKD-506 [49] and CKD-L [50].

DNA methylation is the process by which DNA methyltransferase binds a methyl group to the cytosine 5-carbon position of a CpG dinucleotide in the genome without altering the DNA sequence. The most frequent locations for DNA methylation are CpG islands. DNA methyltransferases (DNMTs), the most significant of which is DNMT1, cause DNA methylation. DNMT1 expression is low and rheumatoid arthritis synovial fibroblasts (RASFs) are hypomethylated. Research has demonstrated that CpG methylation in the IL-6 promoter region can control the pathogenesis of RA in PBMCs of RA patients [51]. Patients with RA have hypomethylated CD4+ T cells, and it has been discovered that CD4+CD8+ T cells have considerably hypomethylated IFNγ promoters, allowing them to release larger amounts of IFNγ [52]. Anti-inflammatory cytokine IL-10 was shown to be more highly expressed in PBMC obtained from patients with RA when treated with the DNMTs inhibitor 5′-AzaC [53]. As a result, DNMT inhibitors have been suggested as possible RA medications.

MicroRNAs play a significant role in the alteration of non-coding RNAs. Patients with RA and different RA-associated cells have distinct variations in miRNA expression. For instance, some miRNAs were shown to be up-regulated (miR-16, miR-103a, miR-132, miR-145, miR-146a, and miR-155) and down-regulated (miR-21, miR-125b, and miR548a) in peripheral blood monocytes from RA patients. These findings may be connected to T-cell homeostasis [54]. Another possible treatment approach for RA is targeting miRNAs. For instance, it has been demonstrated that blocking miR-155 increases FOXO3 and decreases inflammation and FLS proliferation [55]. Targeting miR-146a has also been demonstrated to decrease FLS invasion and migration through the miR-146a/GATA6 axis [56]. Key new therapeutic strategies for the treatment of RA are described in Table 2.

5. Discussion

The new promising treatments for RA described in this review have undeniable advantages over traditional treatments. At the same time, they are characterized by a number of limitations that do not allow their use as the main tool in clinical practice for RA therapy. However, strategies can be proposed to overcome current limitations in the future.

The heightened vulnerability to infections, the need for recurrent injections, and the potential for the development of anti-drug antibodies to result in treatment failure or unpleasant responses are some of the drawbacks associated with the current RD treatments [57]. Similar to how CAR T cell therapy treats cancer, it targets autoantigenic B cells, which trigger autoimmune reactions, without impacting the whole immune system in autoimmune illnesses. Its capacity to produce a targeted and durable remission makes it a viable treatment strategy for autoimmune disorders.

Its usage in RA is found to be restricted, nevertheless, as a single CAR T cell is unable to efficiently target the several autoreactive lymphocyte subtypes that are present in RA patients [58]. Furthermore, pinpointing a particular biological target for the pathogenic CD4+ T cells is a significant obstacle in the use of single-chain variable fragment CAR T cell therapy for autoimmune disorders [34]. To prevent damage to normal tissues, this entails discovering a target that is specific to marking dangerous cells and absent from healthy cells [58]. In order to get around this restriction, research has used strategies that seek to identify autoreactive cells and target them with a single therapy in order to develop a universal CAR T cell therapy. In order to develop a therapeutic that can be given to a larger patient population, the plan is to determine the patient's level of autoantibodies and target the key epitope peptides [58].

The CRISPR-Cas9 technique, in particular, has emerged as a viable option in the treatment of autoimmune illnesses as our understanding of their molecular and immunological causes increases. Potential applications extend beyond common illnesses; treating rare diseases is one area of considerable promise. However, further research in people is required because the majority of the studies to date on the use of CRISPR-Cas9 in the therapy of autoimmune illnesses have been carried out in cell studies. In addition, a number of technical issues must be resolved, including immunological responses, insufficient indel or low homology-directed repair efficiency, off-target activity, and in vivo distribution of the CRISPR-Cas9 system components [59].

Table 2. Key new therapeutic strategies for the treatment of RA.

Therapeutic strategy	Therapeutic action	Exciting limitations
Cell therapy	Disruption of autoreactive B and CD4+ T-lymphocytes	Can be targeted to only single autoreactive cell type
Gene reduction	Knock-out of RA pathogenesis genes (MyD88, TNFAIP3, IL20RA, OLIG3)	Insufficient indel, off-target activity, and *in vivo* distribution of the CRISPR-Cas9 system components
Epigenetic regulation	Inhibition of HDACs, DNMTs and MicroRNAs action	Small amount of clinical evidence

6. Conclusion

Currently used drugs for the treatment of RA, including DMARDs, which can level out the deterioration of the well-being of patients with RA, however, have limitations, which is why the development of new types of drugs is promising. The main treatment strategies for RA include cell therapy, aimed primarily at curbing the proliferation of autoimmune B lymphocytes; gene therapy designed for genetic knockout of genes responsible for the development of inflammation in RA and epigenetic regulation aimed at changing the activity of a number of pathological genes in RA. Studies are showing the effectiveness of these methods in the treatment of RA, but at the same time, large-scale clinical studies are required to prove the feasibility of using these therapies.

Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed consent

The authors declare that no patients were used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request

Authors' contributions

All authors had equal roles in study design, work, statistical analysis and manuscript writing.

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References

1. Tabin S, Gupta R, kamili A, Parray J (2022) Medical and medicinal importance of Rheum spp. collected from different altitudes of the Kashmir Himalayan range. Cell Mol Biomed Rep 2(3): 187-201. doi: 10.55705/cmbr.2022.349901.1050.
2. Fuller DT, et al (2021) Prevalence of Common Comorbidities in Rheumatoid Arthritis in Rural New York Compared With National Data. Cureus 13(11):e19432. doi:10.7759/cureus.19432.
3. Theis KA, et al (2019) Which one? What kind? How many? Types, causes, and prevalence of disability among U. S. adults. Disabil. Health J 12(3):411-421. doi:10.1016/j.dhjo.2019.03.001.
4. Radu AF, Bungau SG (2021) Management of Rheumatoid Arthritis: An Overview. Cells. Multidisciplinary Digital Publishing Institute (MDPI) 10(11). doi:10.3390/cells10112857.
5. Rheumatoid Arthritis Treatment Options | Johns Hopkins Arthritis Center [Electronic resource]. URL: https://www. hopkinsarthritis. org/arthritis-info/rheumatoid-arthritis/ra-treatment/ (accessed: 17. 05. 2024).
6. Benjamin O, et al (2023) Disease-Modifying Antirheumatic Drugs (DMARD). StatPearls. StatPearls Publishing.
7. Bizzaro N, et al (2013) Anti-cyclic citrullinated peptide antibody titer predicts time to rheumatoid arthritis onset in patients with undifferentiated arthritis: results from a 2-year prospective study. Arthritis Res Ther 15(1). doi: 10.1186/ar4148.
8. Van Der Woude D, et al (2010) Gene-environment interaction influences the reactivity of autoantibodies to citrullinated antigens in rheumatoid arthritis. Nat Genet 42(10):814-816. doi:10.1038/ng1010-814.
9. Okada Y, et al (2014) Risk for ACPA-positive rheumatoid arthritis is driven by shared HLA amino acid polymorphisms in Asian and European populations. Hum Mol Genet. Oxford University Press 23(25):6916. doi:10.1093/hmg/ddu387.
10. Goh LL, et al (2017) NLRP1, PTPN22 and PADI4 gene polymorphisms and rheumatoid arthritis in ACPA-positive Singaporean Chinese. Rheumatol Int Rheumatol Int 37 (8):1295-1302. doi:10.1007/s00296-017-3762-x.
11. Stolt P et al (2010)Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis. Ann. Rheum. Dis 69(6):1072-1076. doi:10.1136/ard.2009.114694.
12. Watkin LB, et al (2015)COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis. Nat Genet 47(6) :654-660. doi:10.1038/ng.3279.
13. Konig MF, et al (2016) Aggregatibacter actinomycetemcomitans-induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis. Sci Transl Med 8(369):369ra176. doi:10.1126/scitranslmed.aaj1921.
14. Wegner N, et al (2010) Peptidylarginine deiminase from Porphyromonas gingivalis citrullinates human fibrinogen and α-enolase: Implications for autoimmunity in rheumatoid arthritis. Arthritis Rheum 62(9):2662. doi:10.1002/art.27552.
15. Khandpur R. et al (2013) NETs are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis. Sci Transl Med Sci Transl Med 5(178). doi:10.1126/scitranslmed.3005580.
16. Alspaugh MAet al (1981) Elevated Levels of Antibodies to Epstein-Barr Virus Antigens in Sera and Synovial Fluids of Patients with Rheumatoid Arthritis. J Clin Invest 67 (4):1134. doi:10.1172/jci110127.
17. Van Der Woude D, et al (2010) 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 69(8): 1554-1561. doi:10.1136/ard.2009.124537.
18. Lu MC, et al (2010) Anti-citrullinated protein antibodies bind surface-expressed citrullinated Grp78 on monocyte/macrophages and stimulate tumor necrosis factor alpha production. Arthritis Rheum 62 (5):1213-1223. doi:10.1002/art.27386.
19. Zvaifler NJ, et al (1985) Identification of immunostimulatory dendritic cells in the synovial effusions of patients with rheumatoid arthritis. J Clin Invest 76,(2):789-800. doi:10.1172/JCI112036.
20. Yang Z. et al (2016) Restoring oxidant signaling suppresses proarthritogenic T cell effector functions in rheumatoid arthritis. Sci Transl Med 8 (331). doi:10.1126/scitranslmed.aad7151.
21. Wu F,(2021) et al. B Cells in Rheumatoid Arthritis: Pathogenic Mechanisms and Treatment Prospects // Front Immunol (12). doi: 10.3389/fimmu.2021.750753.
22. Edwards JC (1994) The nature and origins of synovium: experimental approaches to the study of synoviocyte differentiation. J Anat Wiley 184 (3): 493.
23. Filer A. et al (2006) Differential Survival of Leukocyte Subsets Mediated by Synovial, Bone Marrow, and Skin Fibroblasts: Site-Specific Versus Activation-Dependent Survival of T Cells and Neutrophils. Arthritis Rheum. Europe PMC Funders 54(7):2096. doi:10.1002/art.21930.

24. McInnes IB, Schett G (2011) The pathogenesis of rheumatoid arthritis. N Engl J Med 365(23):2205-2219. doi: 10.1056/NEJMra1004965.
25. Pettit AR; et al (2006) RANKL protein is expressed at the pannus-bone interface at sites of articular bone erosion in rheumatoid arthritis. Rheumatology (Oxford) 45 (9):1068-1076. doi: 10.1093/rheumatology/kel045.
26. Verschueren P. et al (2017) Effectiveness of methotrexate with step-down glucocorticoid remission induction (COBRA Slim) versus other intensive treatment strategies for early rheumatoid arthritis in a treat-to-target approach: 1-year results of CareRA, a randomised pragmatic open-label superiority trial. Ann Rheum Dis 76(3): 511-520. doi: 10.1136/annrheumdis-2016-209212.
27. Friedman B, Cronstein B (2019) Methotrexate Mechanism in Treatment of Rheumatoid Arthritis. Joint Bone Spine 86 (3): 301. doi: 10.1016/j.jbspin.2018.07.004.
28. Köhler BM, et al (2019) Current Therapeutic Options in the Treatment of Rheumatoid Arthritis. J Clin Med (MDPI 8 (7). doi: 10.3390/jcm8070938.
29. Sulfasalazine: Uses, Dosage, Side Effects, Warnings - Drugs. com [Electronic resource]. URL: https://www. drugs. com/sulfasalazine. html (accessed: 04. 06. 2024).
30. Cheifetz A, et al (2003) The incidence and management of infusion reactions to infliximab: a large center experience. Am. J. Gastroenterol. Am J Gastroenterol 98 (6):1315-1324. doi: 10.1111/j.1572-0241.2003.07457.x.
31. Bhandari S. (2023) Chimeric antigen receptor T cell therapy for the treatment of systemic rheumatic diseases: a comprehensive review of recent literature. Ann Med Surg 85 (7):3512. doi: 10.1097/MS9.0000000000000891.
32. Bhoj VG, et al (2016) Persistence of long-lived plasma cells and humoral immunity in individuals responding to CD19-directed CAR T-cell therapy Blood 128(3):360-370. doi: 10.1182/blood-2016-01-694356.
33. Zhang B, et al (2021) In vitro elimination of autoreactive B cells from rheumatoid arthritis patients by universal chimeric antigen receptor T cells. Ann. Rheum. Dis. 80(2):176-184. doi: 10.1136/annrheumdis-2020-217844.
34. Whittington KB, et al (2022)CD8+ T cells expressing an HLA-DR1 chimeric antigen receptor (CAR) target autoimmune CD4+ T cells in an antigen specific manner and inhibit the development of autoimmune arthritis. J Immunol 208 (1):16. doi: 10.4049/jimmunol.2100643.
35. Ghobadinezhad F, et al (2022) The emerging role of regulatory cell-based therapy in autoimmune disease. Front Immunol SA13:1075813. oi: 10.3389/fimmu.2022.1075813.
36. Lee MH, et al (2022) Genome Editing Using CRISPR-Cas9 and Autoimmune Diseases: A Comprehensive Review. Int J Mol Sci 23(3). doi:10.3390/ijms23031337.
37. Detection of the novel IL-1 family cytokines by QAH-IL1F-1 assay in rheumatoid arthritis - PubMed [Electronic resource]. URL: https://pubmed. ncbi. nlm. nih. gov/27188731/ (accessed: 18. 06. 2024).
38. Swindell WR (2018) et al. RNA-seq analysis of IL-1B and IL-36 responses in epidermal keratinocytes identifies a shared MyD88-dependent gene signature. Front Immunol S. A9:. 29. doi: 10.3389/fimmu.2018.00080. eCollection 2018.
39. Stahl EA, et al (2010) Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. Nat. Genet. NIH Public Access 42 (6):508. doi: 10.1038/ng.582.
40. Wang S, et al (2016) TALEN-mediated enhancer knockout influences TNFAIP3 gene expression and mimics a molecular phenotype associated with systemic lupus erythematosus // Genes Immun 17(3):165. doi: 10.1038/gene.2016.4.
41. Yang J,et al (2020)Analysis of chromatin organization and gene expression in T cells identifies functional genes for rheumatoid arthritis. Nat. Commun. Nature Publishing Group, 202011(1). doi: 10.1038/s41467-020-18180-7.
42. Wang G,et al (2016) Poster Presentation Abstracts. Int. J. Rheum. Dis. John Wiley & Sons, Ltd19, 21-293.
43. Jing W, et al (2015) CRISPR/CAS9-Mediated Genome Editing of miRNA-155 Inhibits Proinflammatory Cytokine Production by RAW264. 7 Cells. Biomed Res. Int. Hindawi Limited. doi: 10.1155/2015/326042.
44. Jia W, et al (2018) Histone demethylase JMJD3 regulates fibroblast-like synoviocyte-mediated proliferation and joint destruction in rheumatoid arthritis // FASEB J. 32:4031-4042. doi: 10.1096/fj.201701483R.
45. Wu W,et al(2019) Cystathionine-γ-lyase ameliorates the histone demethylase JMJD3-mediated autoimmune response in rheumatoid arthritis. Cell Mol Immunol 16:694. doi: 10.1038/s41423-018-0037-8.
46. Angiolilli C, et al (2016) Inflammatory cytokines epigenetically regulate rheumatoid arthritis fibroblast-like synoviocyte activation by suppressing HDAC5 expression. Ann Rheum Dis. NIH Public Access75:430. doi: 10.1136/annrheumdis-2014-205635.
47. Göschl L. et al (2020) Histone deacetylase 1 (HDAC1): A key player of T cell-mediated arthritis. 108. doi: 10.1016/j.jaut.2019.102379.
48. Chung YL, et al (2003) A therapeutic strategy uses histone deacetylase inhibitors to modulate the expression of genes involved in the pathogenesis of rheumatoid arthritis. Mol Ther 8(5):707-717. doi: 10.1016/s1525-0016(03)00235-1.
49. Park JK, et al (2020)Therapeutic potential of CKD-506, a novel selective histone deacetylase 6 inhibitor, in a murine model of rheumatoid arthritis. Arthritis Res Ther 22(1). doi: 10.1186/s13075-020-02258-0.
50. Oh BR, et al (2017) Therapeutic effect of a novel histone deacetylase 6 inhibitor, CKD-L, on collagen-induced arthritis in vivo and regulatory T cells in rheumatoid arthritis in vitro. Arthritis Res Ther (1). doi: 10.1186/s13075-017-1357-2.
51. Nile CJ. et al (2020)Methylation status of a single CpG site in the IL6 promoter is related to IL6 messenger RNA levels and rheumatoid arthritis. Arthritis Rheum 58(9):2686-2693. doi: 10.1002/art.23758.
52. Pieper J. et al, (2014) Peripheral and site-specific CD4+CD28null T cells from Rheumatoid Arthritis patients show distinct characteristics. Scand J Immunol 79(2):149. doi: 10.1111/sji.12139.
53. Fu LH. et al, (2011) Hypomethylation of proximal CpG motif of interleukin-10 promoter regulates its expression in human rheumatoid arthritis. Acta Pharmacol Sin 32(11):1373. doi: 10.1038/aps.2011.98.
54. Evangelatos G, et al (2019) MicroRNAs in rheumatoid arthritis: From pathogenesis to clinical impact. Autoimmun Rev 18 (11). doi: 10.1016/j.autrev.2019.102391.
55. Liu N. et al (2017) Paeonol protects against TNF-α-induced proliferation and cytokine release of rheumatoid arthritis fibroblast-like synoviocytes by upregulating FOXO3 through inhibition of miR-155 expression. Inflamm. Res Inflamm Res 66(7):603-610. doi: 10.1007/s00011-017-1041-7.
56. Zhao J, et al (2020) Quercetin suppresses migration and invasion by targeting miR-146a/GATA6 axis in fibroblast-like synoviocytes of rheumatoid arthritis // Immunopharmacol. Immunotoxicol. Immunopharmacol Immunotoxicol 42(3):221-227. doi: 10.1080/08923973.2020.1742732.
57. Orvain C, et al (2021) Is There a Place for Chimeric Antigen Receptor-T Cells in the Treatment of Chronic Autoimmune Rheumatic Diseases?Arthritis Rheumatol 73(11):1954-1965. doi:

10.1002/art.41812.
58. Zhang B, et al (2021) In vitro elimination of autoreactive B cells from rheumatoid arthritis patients by universal chimeric antigen receptor T cells. Ann Rheum Dis 80(2):176-184. doi: 10.1136/annrheumdis-2020-217844.
59. Yang Y, et al (2021) CRISPR/Cas: Advances, Limitations, and Applications for Precision Cancer Research // Front. Med. Frontiers Media SA8:649896. doi: 10.3389/fmed.2021.649896.