# Innovative therapeutic strategies in the treatment of rheumatoid arthritis: A review of advances and perspectives

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WORD COUNT 4039
TIME SUBMITTED 16-DEC-2024 01:34PM
PAPER ID 113557595

# Innovative therapeutic strategies in the treatment of rheumatoid arthritis: A review of advances and perspectives

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## ABSTRACT

**Introduction.** Rheumatoid arthritis (RA) is an autoimmune disease associated with chronic inflammation and increased angiogenesis, which leads to joint destruction. Current therapies focus on anti-inflammatory and disease-modifying drugs, with methotrexate being the first-line drug. TNF-α inhibitors, such as adalimumab, are effective but expensive. Research is focusing on new methods such as inhibiting angiogenesis and using nanotechnology for targeted drug delivery, which could revolutionize the treatment of RA by minimizing side effects.

**Materials and methods.** The basis of the work were medical articles collected in PubMed. The research was conducted by analyzing key words such as: "innovative methods of treating

RA", "angiogenesis process in RA", "nanotechnology as treatment of RA", "inflammation pathogenesis", " angiogenesis inhibition".

**Results.** The article discusses innovative therapeutic strategies in the treatment of rheumatoid arthritis (RA), focusing on the role of angiogenesis and the use of nanoparticles. The importance of inhibiting angiogenesis in the synovial membrane is emphasized as a key element in the pathogenesis of RA and a potential therapeutic path. Nanoparticles are presented as a promising method for delivering drugs directly to the site of inflammation, which may reduce systemic side effects.

**Keywords:** new technologies, treatment, rheumatoid arthritis, nanotechnology, perspectives, angiogenesis

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that affects about 1% of adults worldwide, with three women for every one male patient. The disease is most often diagnosed between the 4th and 6th decades of life, but can occur at any age. The progression of the disease and the symptoms it produces are due to its course, which involves increased angiogenesis in the synovial membrane, a chronic inflammatory process, ultimately leading to synovial proliferation and irreversible destruction of the joint. Even small lesions can significantly reduce the patient's quality of life and, over time, prevent participation in social life or cause inability to work. The lesions affect many joints, appear symmetrically and most often affect small joints located distally, in the feet and hands. It has been observed that vascular activity, occurring even during clinical remission, contributes to further cartilage and bone destruction [1].

Current treatments center around anti-inflammatory drugs belonging to the group of NSAIDs, corticosteroids and disease-modifying drugs (LMPChs), among which we distinguish conventionally synthetic (ksLMPChs), targeted synthetic (csLMPChs) and biologics (bLMPChs). Currently, the drugs of first choice are those belonging to the xLMPCh group: methotrexate, leflunomide, sulfasalazine, chloroquine or hydroxychloroquine. They cause alleviation of symptoms and inhibit joint destruction, but their prolonged use is manifested by the occurrence of numerous side effects, affecting the gastrointestinal tract, skin, kidneys and also the immune system [2].

Tumor Necrosis Factor - TNF-α is one of the important elements involved in the pathogenesis of RA, so the therapies carried out most often focus on the use of its inhibitors such as adalimumab or etanercept. The most common treatment options combine the use of methotrexate and the aforementioned biologic drug. This combination has better results than the use of monotherapy, but the overwhelming cost of biologic drugs imposes many restrictions that must be met by a patient seeking to obtain treatment funding [3].

We are therefore looking for newer and newer methods to join, or perhaps replace, current treatments. We are targeting new points of interest that will inhibit the pathogenesis of the disease, as well as new methods of introducing the drug directly into the site of the ongoing disease process, so as to negate the aforementioned side effects as much as possible. For several years now, research has been focused on inhibiting the process of angiogenesis in the synovial membrane - one of the most direct causes of joint destruction [4]. Angiogenesis is the process of creating new blood vessels from existing ones, which occurs through the proliferation of endothelial cells, especially important after birth. It is crucial for many physiological phenomena, such as wound healing and placenta formation, but also for pathological processes, including cancer, ischemic diseases and chronic inflammation. Various mechanisms by which new blood vessels are formed have been discovered, and numerous factors promoting and inhibiting angiogenesis have been identified. Understanding the role of these factors is crucial to the development of new treatments for pathological processes [5]. Another idea appearing in publications in recent years is the use of nanotechnology - the creation of a novel way to deliver a drug directly to the site of the ongoing inflammatory process [6]. A nanoparticle containing the right dose of the drug would act precisely, locally, which would negate systemic side effects [7]. Work on the aforementioned methods is still in progress, but who knows if a breakthrough in the effectiveness of RA treatment will soon be made.

## PATHOGENESIS OF RHEUMATOID ARTHRITIS

RA is classified as a group of systemic, inflammatory and autoimmune diseases that involve the joints and damage the bones. Patients who have genetic risk factors, exposed to environmental risk factors can develop an excessive immune system response. In the first stage, this leads to experiencing symptoms without established arthritis, but can quickly evolve into RA [8]. Some patients at an age before the onset of full-blown RA may already

have autoantibodies such as ACPA (anti-citrullinated protein) or anti-rheumatoid factor (RF) antibodies. These are found in 50-80% of RA patients. [9]. Newly detected antibodies, such as antibodies against carbamylated proteins and antibodies against acetylated proteins, have also been identified in patients [10].

At present, we still do not know the full etiology of RA, but our attention is drawn to the processes associated with immune complexes that occur in the synovial fluid in the joint, during which macrophages release cytokines such as TNFα, interleukin-1 (IL-1) and interleukin-6 (IL-6). Together, they are involved in stimulating the activity of osteoclasts and fibroblast-like synoviocytes (FLS) - highly specialized mesenchymal cells that are found in the synovial membrane and play an active role in arthritis. Both of these processes lead to progressive bone erosion [11].

FLS activation also leads to its production of matrix metalloproteinase (MMP), which leads to cartilage degeneration [12]. FLS also stimulates the NF-κB signaling pathway, which is involved in the pathogenesis of chronic inflammatory diseases. Its activation enables T lymphocytes to bind to proteins on the surface of osteoclasts and thus also promotes bone erosion [13]. FLS migrates from one joint to another, causing RA lesions to characteristically involve symmetrical joints [14].

## INHIBITION OF ANGIOGENESIS IN THE FIGHT AGAINST RA

The process of angiogenesis in RA occurs in response to increased movement of leukocytes, via pre-existing vessels, from the blood to the synovial lining. The chronic and amplifying inflammatory process is an activating factor in the expansion of the vascular network. Angiogenesis consists of several stages, each modified by different factors [15].

In an inflammatory or hypoxic environment, the expression of HIF-1 (hypoxia-inducible factor-1) increases, mediating angiogenesis. HIF-1 is a transcription factor consisting of constitutive expression of a β subunit and an oxygen-regulated α subunit, which mainly determines HIF-1 activation. HIF-1α is rapidly degraded under normal aerobic conditions, but stabilizes under hypoxic conditions when it rapidly translocates to the nucleus, where it induces the expression of vascular endothelial growth factor (VEGF) [16], which, together with fibroblast growth factor (FGF), bind to corresponding receptors on endothelial cells (ECs) and activate these cells to produce proteolytic enzymes. The basement membrane is

then degraded by matrix metalloproteinases (MMPs), leading to migration and further endothelial proliferation into the vascular tubules, which is partially developed by adhesion molecules such as integrins. Finally, blood vessels are stabilized by proangiogenic factors such as Ang1, followed by the incorporation of pericytes into the newly formed basement membrane to facilitate the blood flow process [17].

A good anchor for inhibition of angiogenesis is the VEGF pathway. In the K/BxN transgenic mouse model, treatment with a receptor 1 antagonist (anti-VEGF-RI) resulted in clinical and histological attenuation of the disease throughout treatment. The use of anti-VEGF produced only transient results [18].

One of the most interesting is the treatment with bevacizumab, a humanized monoclonal antibody against VEGF. In a rat model, injections of 30mg/kg weekly over a 2-week period significantly reduced the rate of arthritis, the rate of pathological synovial membrane damage, and serum levels of VEGF and TNFα [19].

The significant impact of hypoxia on the pathogenesis of synovial membrane damage has led to interest in strategies that target HIF-1. Reduction of its expression occurs through certain molecules that act on the cellular cytoskeleton, such as m 2-methoxyestradiol (2ME) and paclitaxel. However, the positive effect of 2ME in arthritis is not necessarily related to inhibition of angiogenesis [20].

Paclitaxel has shown significant suppression of genes for IL-1, IL-6 and IL-8, the release of which is promoted by TNF-α, and which have been shown to play a key role in the process of chronic inflammation in RA. In phase I clinical trials in RA, paclitaxel proved effective and well tolerated [21].

## NANOPARTICLES AS DRUG VECTORS

Nanotechnology is called the ability to study, develop and manage substances at the atomic and molecular levels. Work in this field enables the development of new carrier systems for drug delivery. Precise placement of a drug at the site of an ongoing disease process improves drug profiles such as bioavailability, solubility and diffusivity [22]. The use of nanocarriers in RA therapy will allow for a reduction in doses of currently used drugs while maintaining and even enhancing their effect [23,24] Direct delivery of the drug and also activation of the drug

in the area of synovial inflammation will avoid numerous side effects affecting the whole body, which result from the toxic effects of currently used drugs [25].

An example of such carriers are nanoparticles, colloidal systems up to 100 nm in diameter in which the therapeutic agent is entrapped. Nanoparticles are characterized by a very small size, but a high surface charge and a high surface-to-weight ratio. These properties mean that drug molecules trapped inside are not subject to standard pharmacokinetic rules [26].

[27] In the present study, nanoparticles consisting of linear β-(1,3)-glucans from yeast (BYG) with high affinity for macrophages were formed and methotrexate was introduced into them. BYG-based nanoparticles loaded with methotrexate were then grafted with methoxypoly (ethylene glycol) (mPEG), and its cross-linked form, a copolymer (cBP), was obtained. These molecules loaded with methotrexate targeted macrophages of the inflamed synovial membrane and significantly reduced the secretion of pro-inflammatory cytokines. Due to their treatment effects, as well as their safety of use, methotrexate-loaded nanoparticles (cBPMs) may be used as a clinically safe treatment for RA in the future.

Another drug nanocarriers produced were based on modified cyclodextrin and aimed to deliver dexamethasone phosphate. The particles were 120 nm in size and were hydrophobic due to solvent evaporation in the emulsion. They were characterized by exceptional uptake efficiency and excellent stability. Pharmacokinetic studies showed that the molecules had a high affinity for inflamed synovial membranes. Pharmacodynamics' tests also showed good efficacy, a decrease in inflammatory cytokine levels in the systemic circulation and an improvement in arthritis scores in the absence of drug side effects [28].

In the treatment of RA, combining substances with different mechanisms of action is particularly successful. Gelatin nanoparticles were loaded with glycyrrhetinic acid (GA) and then coated with budesonide conjugated to polycaprolactone conjugated to aminocellulose (PCL-AC). The nanoparticles formulated in this way showed activity against erythema, synovitis, cartilage destruction by reducing B-lymphocyte infiltration and restoring synovial tissue on radiographic examination. The delayed and prolonged release of the drug as well as the nanoparticles' ability to regulate inflammatory mediators contribute to a better therapeutic effect on RA with respect to free drug molecules [29].

## GOLD NANOPARTICLES

Conventional nanoparticles work well for effective therapy, but researchers are increasingly opting for gold nanoparticles (GNPs). They show good biocompatibility, can be produced in different shapes and sizes as needed, are easy to obtain and show high drug loading capacity. All this translates into greater efficacy and stability in drug delivery [30]. In addition, they do not exhibit cytotoxic effects and serious side effects, making them a safe alternative and giving them great potential for application in medicine.

Moreover, GNPs can be used as nanoprobes and contrast agents in the diagnosis of RA [31].

GNPs are not only a good drug carrier, they can also be a drug in their own right and positively influence treatment. Studies have shown that GNPs can bind to vascular endothelial growth factor (VEGF), which has anti-angiogenic effects. GNPs are also an important antioxidant that promotes osteogenesis and stem cell proliferation, and inhibits RANKL-induced osteoclast production. By its action, it reduces bone erosion and cartilage destruction, and lowers inflammation [32].

The use of plasmonic gold nanoparticles containing methotrexate caught the researchers' attention [33]. The surface plasmons on them cause electromagnetic wave amplification. The created nanoparticles can be used, among other things, in magnetically directed chemo-photothermal treatment. The study used mice that were administered the created nanoparticles. In vivo MR images showed their accumulation in inflamed joints, which was enhanced under the influence of an external magnetic field. The rate of methotrexate release from the nanoparticles, in turn, was affected by the use of Near InfraRed (NIR) radiation. The use of both NIR irradiation and an external magnetic field also resulted in higher therapeutic efficacy despite the use of a lower dose of methotrexate contained in the nanoparticles, compared to conventional treatment [34].

## SUMMARY AND CONCLUSIONS

As research conducted into new treatments for rheumatoid arthritis progresses, our chances of finding the most effective treatment possible are becoming better. With new sticking points, we are avoiding many side effects while increasing the effectiveness of therapy without having to keep increasing the necessary doses of medication.

In this article, the authors focus primarily on the process of angiogenesis, one of the key elements of RA pathogenesis. Inhibition of this process offers new prospects for treatment, alleviates the symptoms of already existing disease and accelerates the process of tissue regeneration.

The use of nanotechnology, specifically the use of nanoparticles as drug carriers, is also a novel approach to RA therapy. The new form of administration of already known disease-modifying drugs, inhibiting inflammatory processes, and promoting regeneration of damaged tissues will result in a significant improvement in their bioavailability. The use of drug carriers facilitates the transport of the drug directly to the site of the ongoing disease process, which offsets the harmful systemic effects, while allowing the use of smaller doses to achieve the same or better effect.

A special faction of nanotechnology is the use of gold nanoparticles, which, due to their properties such as relative ease of manufacture, their ability to bind to agents found in the human body, and their antioxidant properties, perform even better in studies than conventionally used carriers. Due to their greater stability and stronger affinity, they better target the site of an ongoing inflammatory process.

The conclusions of this article underscore the importance of seeking further novel solutions and the potential of new approaches to treat RA, noting the need for further research to fully understand mechanisms of action and optimize treatments. As an autoimmune disease with multiple substrates of pathogenesis, RA has posed considerable difficulty in treating and controlling its course, but with the development of science and the finding of new and unique points of interest, we are getting one step closer to fully understanding and completely controlling it. It is possible that it will be a long time before we can fully understand the reasons behind such a course of rheumatoid arthritis, as well as why we so often encounter patients who are affected by it. As we look for newer and newer solutions, we are concerned with improving the comfort of patients' lives, as well as reducing the cost of their long-term treatment. The most important goal of current research into novel treatments for RA should be, first and foremost, the search for a method that meets the above two criteria so that they can be accessible to all.

**Authors' contributions:**

Conceptualization, Karolina Parzęcka, Piotr Kucharczyk, Michał Symulewicz; methodology, Olaf Domaradzki; software Michał Symulewicz; check, Mateusz Michalak; formal analysis,

Bartłomiej Kusy, Mateusz Michalak; investigation, Piotr Kucharczyk ; resources, Karolina Parzęcka; data curation Michal Symulewicz; writing - rough preparation, Karolina Parzęcka, Piotr Kucharczyk; visualization, Michal Symulewicz, Mateusz Michalak; writing – review and editing, Piotr Kucharczyk; supervision, Karolina Parzęcka; project administration, Olaf Domaradzki;

All authors have read and agreed with the published version of the manuscript.

The study did not receive specific funding.

Data presented in this study are available upon request from the author

correspondence.

The authors of this paper report no conflicts of interest.

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