RESEARCH PAPER

Integrating Preclinical Pharmacology, Clinical Trial Data, and Societal Perspectives in the Development of Tofacitinib Vesicular Systems for Rheumatoid Arthritis

Shivani Pannu[1,2], Ankita Sharma[3], Pooja[2], Reena[2], Rekha[4], Davinder Kaur[5], Johny Lakra[1], Rahul Sharma[2], Inderjeet Verma[1*]

[1]MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala, Haryana, India

[2]Gateway College of Pharmacy, Sonipat, Haryana - 131001

[3]School of Pharmaceutical Sciences, Starex University, Gurugram, Haryana - 122413

[4]Bhagwan Mahaveer Institute of Medical Sciences, Sonipat, Jagdishpur, Sonipat - 131030

[5]School of Pharmaceutical Sciences, CGC University, Mohali, Punjab - 140307.

Email: davinder13021997@gmail.com

[*]Corresponding Author: Dr. Inderjeet Verma, Professor, MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala, Haryana, India. Email: indupup@gmail.com

ABSTRACT

The typical manifestations of rheumatoid arthritis (RA) are persistent inflammation, joint destruction, and poor quality of life caused by a chronic and debilitating inflammatory disease. Although biologic and traditional DMARDs have developed, new treatment options are necessary based on the disadvantages of immunogenicity, high cost, and lack of response in patients. Tofacitinib, an oral Janus kinase (JAK) inhibitor, is a biological treatment that can offer a personalized therapy by modifying the JAK-STAT signalling pathway; however, it has pharmacokinetic limitations, systemic adverse effects, and limited tissue distribution. New avenues of tofacitinib distribution optimization have been enabled by the recent developments in nanomedicine, namely, in the field of vesicular drug delivery systems, including liposomes, niosomes, transferosomes, and ethosomes. These carriers provide a link between preclinical pharmacology and clinical translation with enhanced bioavailability, enhanced pharmacological activity, reduced systemic toxicity, and controlled release. The long-term effectiveness and tolerable safety profile of Tofacitinib is supported by clinical trial results supported by real-world evidence and its capacity to enhance patient compliance and medical cost-effectiveness is indicated by social and economic analyses. This review identifies that tofacitinib-based vesicular systems can transform the way RA is treated and direct future research in the area of personalized medicine and nanotherapeutics because they incorporate preclinical, clinical, pharmacological, and societal insights.

Keywords: Rheumatoid arthritis, Tofacitinib, JAK-STAT pathway, Vesicular drug delivery, Nanomedicine, Pharmacology, Clinical trials, Patient outcomes, Healthcare economics

How to cite this article: Pannu S, Sharma A, Pooja, Reena, Rekha, Kaur D, Lakra J, Sharma R, Verma I. Integrating Preclinical Pharmacology, Clinical Trial Data, and Societal Perspectives in the Development of Tofacitinib Vesicular Systems for Rheumatoid Arthritis. Int J Drug Deliv Technol. 2026;16(19s): 1023-1033. DOI: 10.25258/ijddt.16.19s.117

Source of support: Nil.

Conflict of interest: None

1. Introduction

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disease that still poses a major burden to society and health systems everywhere. Recent epidemiological studies indicate that 17.6 million individuals were affected in 2020, and the levels may increase to 32 million in 2050(1). RA remains one of the leading causes of disability, with a reported disability-adjusted life years (DALYs) of more than three million in the global statistics, although age-specific death rates have decreased due to progress in therapies.(2). The disease also has significant social and financial implications besides compromising physical functionality in low- and middle-income countries, where access to advanced treatment remains skewed and access to healthcare resources is limited.(3). With more treatment choices available and earlier diagnosis, patients in high-income countries experience a better quality of life and disease management than patients in resource-limited areas, where there is both a delay in treatment and increased disability rates.(4). Regional disparities ensure that

creative cures are necessary. Traditional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, remain the first-line therapy because of their low price, but the success rates are inconsistent, and adverse effects often make them difficult to use over time.(5). Biologic agents and synthetic DMARDs based on targets (including Janus kinase [JAK] inhibitors like tofacitinib) offer greater efficacy and faster disease control(6). They are, however, limited in popularity due to their prohibitive price, regulatory and safety-related issues, including potential infections, and variability in patient response.(7). Also, lifestyle, comorbidity, and genetic predispositions have a major role in the outcome of the treatment, and the problem of personalized treatment persists.(8). The economic consequences are large, with direct treatment costs in low and middle-income countries as low as between 235 and over 2,000 dollars per year per patient and indirect costs of decreased productivity, disability, and quality of life.(9). The following developments precondition the possibility of controlling the disease more accurately and efficiently, decreasing the number of doses, eliminating the effects of the system on the whole organism, and improving the adherence of patients(10). Despite these developments, however, there are issues to be addressed before the laboratory discoveries can be applied to clinical practice, especially in terms of mass production, long-term reliability, cost-efficiency, and adherence.(11). The introduction of nanomedicine into the treatment of RA in the coming decade is such a radical step; however, to bridge the gap between the efficacy of the pharmaceuticals, the clinical results, and the social demands.(12).

2. Pharmacological Landscape of Tofacitinib in RA

To suppress the JAK-STAT signalling pathway, which coordinates the production of pro-inflammatory cytokines and immunological activation to trigger rheumatoid arthritis (RA), tofacitinib, the first oral Janus kinase (JAK) inhibitor licensed in the treatment of rheumatoid arthritis (RA), mainly acts on JAK1 and JAK3 and has minor effects on JAK2 and TYK2(13). Tofacitinib (with a short half-life of about three hours and two-daily dosage (but an extended-release formulation is available); requires twice-daily dosing (although some studies have found baricitinib (JAK1/2) to be more effective); rapidly absorbed (bioavailability = 74%); and metabolized by CYP3A4/CYP2C19), its pharmacokinetics demonstrate dose-dependent inhibition of STAT phosphorylation and markedly reduces CRP and disease activity scores(14). The safety profile of tofacitinib, which contains side effects like infections, herpes zoster, anemia, neutropenia, and cardiovascular issues, must be thoroughly considered regardless of its clinical needs(15). Cancers and cholesterol victories that lead to FDA and EMA warnings, particularly in old patients and those with heart problems(16). On the whole, tofacitinib is one of the most important improvements in the treatment of RA because it offers a rapid-acting oral alternative to biologic therapy(17). Nonetheless, due to its rather wide JAK inhibition profile, it must be carefully patient-selected and monitored to find a balance between safety and efficacy because of the relative pharmacological differences between JAK inhibitors as listed in Table 1(18).

Table 1. Comparative Pharmacological Profile of JAK Inhibitors in Rheumatoid Arthritis (RA)

Parameter	Tofacitinib (JAK1/3 ± JAK2)	Baricitinib (JAK1/2)	Upadacitinib (JAK1)	Filgotinib (JAK1)
Oral Bioavailability	~74%	~79%	~70%	~50%
Half-life	~3 hrs	~12 hrs	~14 hrs	~7 hrs
Dosing Frequency	BID (XR: QD)	QD	QD	QD
Clinical Efficacy	Broad, effective in MTX-IR RA	Strong DAS28 reduction	Superior to adalimumab in MTX-IR	Good ACR responses
Common Adverse Effects	Infections, anemia, zoster	Infections, VTE risk	GI upset, infection	Fatigue, infection
Regulatory Concerns	CV events, malignancy risk	Thrombosis, lipid changes	Safety favorable, long-term data emerging	Reproductive toxicity

3. Mechanistic Basis of JAK-STAT Pathway Inhibition by Tofacitinib

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway is a central mediator of the effects of various pro-inflammatory cytokines, including interleukin-6, interferons, and

granulocyte-macrophage colony-stimulating factor, in the pathophysiology of rheumatoid arthritis (RA)(19). Under normal physiologic conditions, cell-surface receptor binding of cytokine leads to the activation of receptor-associated JAK isoforms (JAK1, JAK2, JAK3, and TYK2), which phosphorylate the STAT proteins(20). Tofacitinib interrupts downstream phosphorylation of STATs and inhibits the expression of inflammatory genes by selectively blocking JAK1/JAK3 and partially blocking JAK2/TYK2, and accordingly leads to the dimerization and translocation of these phosphorylated STATs to the nucleus, thereby increasing synovial inflammation, pannus development, and joint degradation(21). This mechanism decreases synovial inflammation by decreasing the production of inflammatory mediators, including TNF-alpha, IL-6, and IL-1beta, and enhances clinical outcomes. Importantly, the broad JAK inhibition of tofacitinib is an additional difference to biologics that prevent the effects of single cytokines, allowing the inhibition of multiple cytokine pathways at once. However, the consequence of this common practice is also adverse in the form of increased susceptibility to infections and hematologic changes(22). Figure 1 recaps the molecular mechanisms underlying tofacitinib inactivation of the JAK-STAT pathway and highlights the mechanism through which it acts to regulate immunological dysregulation in RA(23).

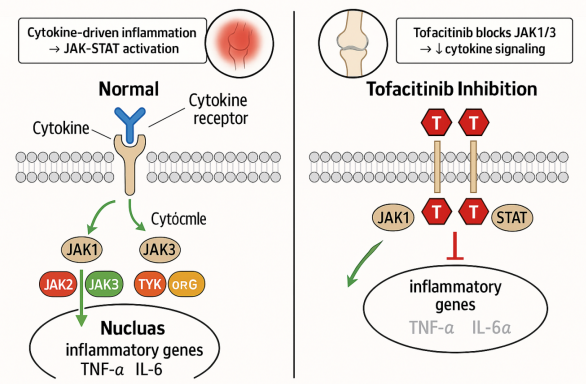
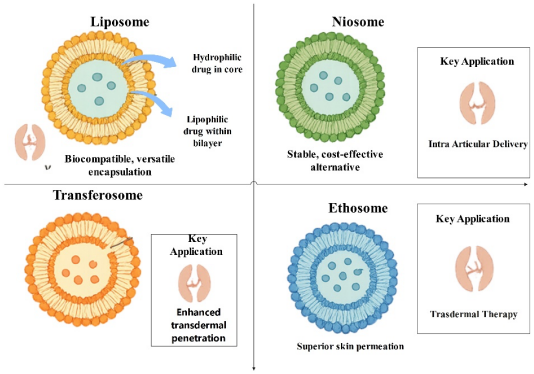


Figure 1. Mechanistic illustration of JAK-STAT pathway inhibition by tofacitinib in rheumatoid arthritis.

Schematic representation of JAK-STAT signalling in rheumatoid arthritis. The left panel illustrates normal cytokine-driven activation leading to inflammatory gene transcription. The right panel shows Tofacitinib-mediated inhibition of JAK1/3, suppressing STAT activation and reducing pro-inflammatory gene expression.

4. Vesicular Drug Delivery Systems in Rheumatoid Arthritis

Overcoming these limitations of traditional formulations, vesicular drug delivery systems have become highly promising to improve the treatment outcome of rheumatoid arthritis (RA)(24). These nanoscale carriers, which comprise liposomes, niosomes, transferosomes, and ethosomes, enhance the solubility, stability, and site-specific targeting by encapsulating hydrophilic and lipophilic drugs in lipid/surfactant-based bilayers(25). Liposomes are one of the most studied since they are biocompatible and able to transport medications directly to inflammatory tissues of the synovia due to their ability to make bilayers out of phospholipids. Conversely, niosomes (non-ionic surfactants) are more stable and cheaper than liposomes(26). Due to their deformation properties, transferosomes permit greater tissue penetration and efficient transdermal penetration, which would be attractive in regard to non-invasive treatment of RA(27). When compared to conventional oral or intravenous delivery of JAK inhibitors such as tofacitinib and disease-modifying antirheumatic medications (DMARDs), which, in many cases, have low bioavailability, systemic toxicity, and off-target effects, such vesicular carriers have several advantages(28). Vesicular systems contribute to superior therapeutic effect and reduce gastrointestinal, hepatic, and hematological side effects by leading to control and sustained release, prolonged circulation, and preferential accumulation in inflammatory joints due to the superior permeability and retention (EPR) effect(29). Also, they serve as the precursors to various modes of administration, such as transdermal or intra-articular injection, that improve patient compliance to long-term therapy, but these limitations are slowly being overcome through the rapid development of nanotechnology, novel lyophilization technology, scale-up processes using microfluidics, and complex stability control agents, which are simplifying the transition of vesicular carriers into clinical practice(25). By combining all these factors, vesicular systems will present a radical solution to RA therapy by integrating increased safety, patient-centrism, and precise delivery that can have the potential to redefine the future of treatment(30). Figure 2



5. Preclinical Evaluation of Tofacitinib-Loaded Vesicular Systems

Recently, preclinical studies of tofacitinib-loaded vesicular systems have gained rapid attention as researchers consider approaches grounded in nanomedicine to circumvent the pharmacological limitations of traditional formulations(31). This process is still based on the optimization of the formulation, in which the ratio of lipid to drug, choice of phospholipid or surfactant, hydration strategies, sonication or extrusion, are altered to achieve the desired zeta potential, polydispersity index (PDI), and particle size(32). Optimized vesicles have a nano-range (less than 200 nm), narrow PDI (less than 0.3), and stable surface charge, all of which are essential to long-term circulation, high drug loading, and site-specific delivery in inflammatory joints(33). Encapsulation efficiency often exceeds 7085% in in vitro assays, and controlled and extended-release profiles of up to 2472hours reduce dose frequency compared to free tofacitinib. Stability tests solve a significant shortcoming of the conventional small-molecule formulations, and indicate that lyophilized vesicular formulations preserve their structure and therapeutic functionality during extended storage(34). Preclinical research with well-established animal models of rheumatoid arthritis, including mice with collagen-induced arthritis (CIA) or rats with adjuvant-induced arthritis (AIA), is used to determine the efficacy of treatments before transitioning to in vivo research (e.g., reduced paw swelling, reduced pro-inflammatory cytokines (TNF-α, IL-6, IL-1-β), and histological evidence of joint protection). Importantly, these vesicular devices also reduce systemic toxicity by providing targeted effect and delayed release to reduce off-target effects commonly associated with oral tofacitinib(35). As an illustration, encapsulation has been shown to minimize the risk of hepatotoxicity and immunosuppression because it minimizes unnecessary systemic exposure(36). Translational Preclinical pharmacokinetic data support the translational potential of these systems by showing increases in bioavailability, half-life extension, plus enhanced accumulation in inflammatory synovial tissues, in addition to efficacy(37). Translational Preclinical data support the translational potential of the systems, showing increased bioavailability, half-life extension, and increased accumulation in inflammatory synovial tissues on top of efficacy(38). Nevertheless, the long-term safety profiles and batch-to-batch variation need to be well validated, so scalability, repeatability, and regulatory concerns remain a critical barrier to clinical translations. Combined, preclinical research provides good evidence that tofacitinib-loaded vesicular systems have the potential to address unmet needs in the management of rheumatoid arthritis by integrating pharmacological efficacy and an increased margin of safety(38). This opens up to future clinical studies and ultimate inclusion into the treatment protocols(38). Table2

Table 2. Preclinical Studies on Tofacitinib Vesicular Systems

System	Model	Key Features	Findings	Safety	Year
Liposomes	CIA mice	~150 nm; EE 82%	↓ paw swelling, ↓ TNF-α/IL-6, joint protection	↓ hepatotoxicity	2024
Niosomes	AIA rats	~180 nm; EE 78%	Sustained release, improved mobility	↓ GI irritation	2024
Transferosomes	Synoviocytes + CIA mice	<120 nm; deformable	↑ uptake, STAT inhibition	Safe at therapeutic dose	2025
Ethosomes	AIA rats (topical)	~140 nm; ethanol	Better skin penetration,	↓ systemic effects	2025

		vesicles	anti-inflammatory		

6. Clinical Trial Evidence and Real-World Data

Empirical evidence and clinical trials have given a clear insight into Tofacitinib and its effectiveness, safety, and translational usefulness in rheumatoid arthritis (RA)(39). Tofacitinib, as a single agent or used in combination with methotrexate, has shown substantial clinical benefits in disease activity, physical functioning, and quality of life in a broad range of Phase II -IV clinical trials worldwide.(39). According to landmark trials in which Tofacitinib was tested, such as ORAL Scan, ORAL Strategy, and ORAL Step, Tofacitinib showed comparable efficacy to the biologics, adalimumab, a quick onset response, and durable ACR20/50/70 responses in a variety of patient demographics.(40). Comparative studies with biologics and with conventional DMARDs confirmed that tofacitinib is an effective oral substitute that is comparable in effect to tumor necrosis factor (TNF) inhibitors.(41). This renders it particularly appealing to patients who opt against the use of injections. However, the issue of safety remains significant in deciding on its therapeutic role.(42). The most noticeable adverse events during trials were infections and specifically herpes zoster, and thromboembolic and cardiovascular events in the high-risk groups.(43). Consequently, regulators focus on being vigilant and select patients on a case-by-case basis to enhance the risk-benefit ratio.(42). In addition to trial data, tofacitinib demonstrated significantly higher disease management and functional improvements in routine therapy through real-world evidence on registries such as CorEvitas (US) and other European cohorts.(44). Persistence rates, often affected by patient comorbidities, past biologic exposure, and physician preference, were slightly lower than those of TNF inhibitors.(45). The efficacy of the latter was re-established by recent meta-analyses addressing observational studies and randomized controlled trials, and evidenced tolerable safety risks in case of prudent use in patients.(45). In summary, these findings indicate that tofacitinib has found a niche in the RA treatment regimen due to its biologic efficacy, sustained benefits, and growing evidence.(46). They also emphasize, though, the importance of pharmacovigilance and meticulous selection of the patients (Table 3).

Table 3. Major Clinical Trials of Tofacitinib in Rheumatoid Arthritis

Trial	Phase / Population	Key Outcomes	Safety Notes	Year
ORAL Scan	Phase III, MTX-inadequate RA	↓ Structural damage, ↑ ACR responses	Infections, GI effects	2024
ORAL Strategy	Phase III, biologic-naïve RA	Non-inferior to adalimumab + MTX	Herpes zoster risk	2024
ORAL Step	Phase III, anti-TNF inadequate	Significant ACR20/50/70 improvement	↑ Serious infections	2025
LTE Studies	Long-term extension (global)	Sustained efficacy >5 years	Thromboembolic risk	2025

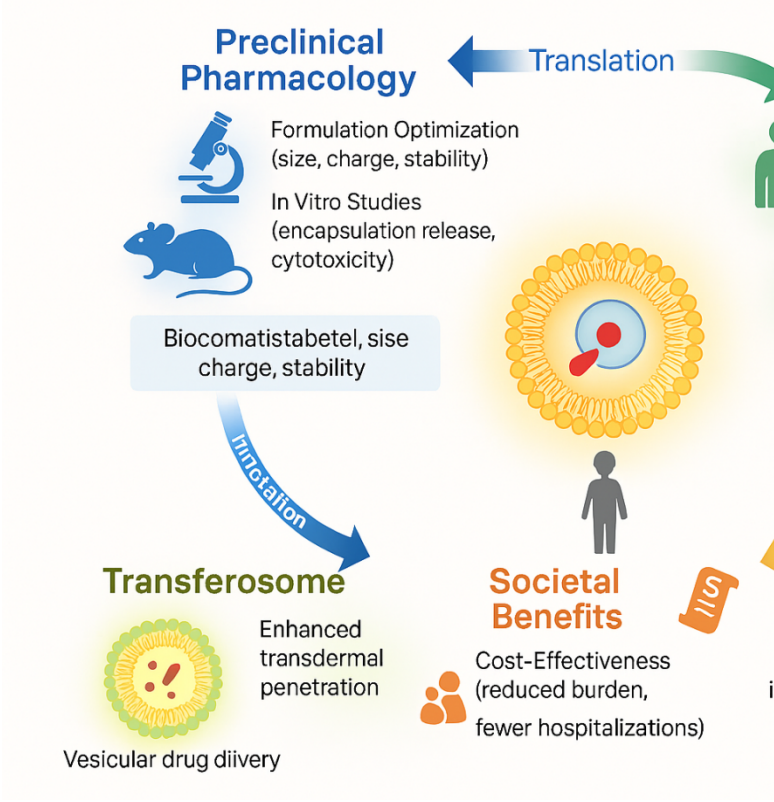
7. Societal and Economic Dimensions of Tofacitinib Therapy

Tofacitinib treatment of rheumatoid arthritis (RA) has social and economic implications as well as pharmacological effects, which leads to an interest in the problems of affordability, accessibility, adherence, and health policy.(47). The general opinion is that tofacitinib is cheaper than the biologic drugs like adalimumab in developed economies, including the US, and in some parts of Europe.(48). The main reasons behind this are the oral nature of its intake, the lack of necessity concerning the intake of administration in a hospital in the IV form, and the lower cost of monitoring.(49). The analysis of cost-effectiveness conducted on international marketplaces, on the other hand, has never given an all-encompassing picture.(50). Nevertheless, the problem of patient compliance has existed even in low- and middle-income nations where generic medicines and health care services are scarce. Delivery in oral format is more convenient and increases compliance with injectable disease-modifying antirheumatic drugs (DMARDs), resulting in better disease control and lowered health care costs in the long run.(51). Its broader social benefit is also supported by practical research where an immense improvement in the quality of life was reported, with the patients describing a higher mobility, a rise in work productivity, and an improvement in

psychosocial well-being.(52). However, there are some differences, especially in those environments where resources are scarce, insurance is low, and out-of-pocket costs are high, resulting in underutilization even where treatment is required.(53). The views on healthcare policy change depending on the need to reach a compromise between innovation and sustainability as payers and insurers reflect on the initial spending on tofacitinib and the potential future benefits in the shape of reduced disability, reduced hospitalization, and reduced reliance on corticosteroids(54). Inequality in distribution, namely in rural or poor societies, uneven reimbursement policies, and split regulatory licenses are also contributing to the aggravation of access problems. Outcome-based contracts, levels of payment, or national formularies using JAK inhibitors have been adopted by several countries in an effort to rationalize equitable access.(55). Safety-related regulatory warnings have also been observed to impact the prescribing and reimbursement patterns, some of which are associated with cardiovascular and cancer safety, whereby the chosen parameters have been limited, or a prior biologic failure pre-licensure has occurred.(56). The economic price of the tofacitinib therapy must then be placed in a wider context of healthcare equity, individual-based treatment that can be attained by cost-cutting, insurance, and international standardisation of accessibility, in the social and cultural context.(57).

8. Integrative Translational Framework: From Bench to Bedside

Patient-centred treatments also favor this mechanism of translating, where adherence, quality-of-life improvements, and individualized treatment plans with take patient preferences and socioeconomic factors into account to make therapeutic decisions are in support(58). Tofacitinib is a pharmacological innovation that the vesicular nanocarriers bring; its clinical potential of tofacitinib to diminish the effects of RA, the social benefits involved, such as increased productivity, decreased disability, and lowered health care costs, should also be put into consideration to weigh the impact of tofacitinib therapy(59). Figure 3 theoretically illustrates this multi-layered structure by the preclinical pharmacological data being input into the main clinical evidence domain (Phase II -IV trials, safety assessments, and comparative studies) on the left, feeding. Second, the translation continuum graphic indicates the contribution of vesicular system innovation, which acts as a communication between the initial laboratory results and the actual patient and societal outcome, taking into account the value in society (cost-effectiveness, patient adherence, quality of life, and healthcare policy)(60). This paradigm reinforces the need to engage pharmacologists, physicians, policy makers, and patients in interdisciplinary collaboration with an effort to achieve the fullest therapeutic potential of tofacitinib vesicular systems in RA(61). The Nanomedical research would accelerate the use of nanomedical approaches through the systemic convergence of the pharmacological breakthrough in conjunction with the clinical and social acceptance(62). It will guarantee that laboratory innovations can be cost-effective, effective, and sustainable therapy to address the global burden of RA (Figure 3).



9. Future Perspectives and Research Directions

Convergence of personalized methods, combined therapeutic approaches, and advanced nanomedicine can serve as a hope in the management of rheumatoid arthritis (RA)(63). The following are next-generation nanocarriers under development to enable drugs to be released into inflammatory synovial tissue with precision in response to pH, temperature, or enzyme activity: stimuli-responsive liposomes, polymeric micelles, dendrimers, and hybrid vesicular systems(64). These platforms aim to address the disadvantages of conventional vesicles by improving stability, more specific targeting of inflammatory joints, and the ability to continuously release to

reduce the frequency of dosing(65). In response to the development of personalized medicine approaches, drug delivery systems may be tailored to the genetic, immunological, and metabolic unique characteristics of a patient. Such systems can be guided by biomarkers that indicate therapy response(66). Such individualized therapy will help decrease side effects and optimize the treatment outcome, particularly in patients with comorbidities or in refractory disease(67). Another viable alternative is to integrate nanocarriers with biologics and already existing DMARDS(68). The combination drug therapy could be synergistic, enhancing the action of the immunomodulation process and decreasing the concentration of the respective drugs, thereby lowering the toxicity and expense(69). This combinatoric is best suitable in patients who respond incompletely or not to the current monotherapies. Nonetheless, the developments have many ethical, legal, and long-term safety issues(70). The issue of nanocarrier complexity also involves immunogenicity, systemic bio-distribution, clearance activity, and unknown system effects in chronic delivery, and to work out special legal rules and insurance models(70). Patient education and informed consent ethical considerations will be very important when unveiling the new nanocarrier-based therapies in the clinical setting. Large safety registries, real-life cross-national pharmacovigilance trials, and global standardization of nanomedicine regulation will be required to facilitate both effective, affordable, and safe RA care in the long term(71). All these areas of research are allusions to the paradigm shift in precision nanomedicine research, wherein the long-term advancement of treatments requires convergence of the clinical translation, scientific development, and even the social responsibility.

10. Conclusion

The combination of clinical data and pharmacological data regarding the radical features of tofacitinib in the scenario when it is incorporated into complex vesicle structures to cure rheumatoid arthritis (RA). Tofacitinib selectively stimulates the JAK-STAT signal-transduction pathway, which explains its mechanistic selectivity as a therapeutic agent. Entrapping in vesicular carriers can greatly reduce its pharmacokinetic limitations, e.g., short half-life and systemic toxicity. Preclinical evidence of improved bioavailability and target distribution, and clinical trial evidence of prolonged effectiveness and safety risk manageable, has been used to support the translational potential of these systems. The translational potential of tofacitinib therapy with pharmacology is highly significant in response to patient compliance, improvement of quality of life, and healthcare-system cost-effectiveness. In resource-deprived environments, though, the price-and-access question is still available. Tofacitinib-based vesicular systems need a complex strategy to implement in the future that would involve proper preclinical testing, successful clinical trial proofs, and an equitable health policy prototype. It is also necessary to focus on the study of separate delivery systems, the second generation of nanocarriers, and the pharmacovigilance of long-term safety. To deliver the therapeutic promise of tofacitinib-loaded vesicular systems beyond the laboratory and the clinic walls and to feel it, or experience it, in healthcare delivery worldwide,

Ethical Approval: - No ethical approval in this study
Consent to Participate: - Yes
Consent to Publish: - Yes
Funding: No Source of Funding
Competing Interests: No Competing Interests
Availability of data and materials: All data is available in the manuscript file**.**
Conflict of Interest- No conflict of interest

Reference

1. Manji H, Sisodiya S. Global Burden of Neurological Disease and the Neurology of Climate Change. Neurology: A Queen Square Textbook. 2024:1-15.
2. Yu D-T, Li R-X, Sun J-R, Rong X-W, Guo X-G, Zhu G-D. Global mortality, prevalence, and disability-adjusted life years of Alzheimer's disease and other dementias in adults aged 60 years or older, and the impact of the COVID-19 pandemic: a comprehensive analysis for the global burden of disease 2021. BMC Psychiatry. 2025;25(1):503.
3. Khadija A, Korsah KA, Farhan AA. Parents' Perspectives on the Quality of Life of Adolescents living with Autism Spectrum Disorder in Ghana. Women and Children Nursing. 2025.
4. Talari K, Pathak H, Jain N, Ravindran V. Access to rheumatologic care in tropical regions: Barriers and solutions. Best Practice & Research Clinical Rheumatology. 2025:102052.
5. Shakeel L, Shaukat A, Khaliq N, Kashif A, Mujeeb A, Adnan Z, et al. Rheumatoid arthritis: a comprehensive overview of genetic markers, emerging therapies, and personalized medicine. Annals of Medicine and Surgery. 2025;87(2):696-710.
6. Favalli EG, Maioli G, Caporali R. Biologics or Janus Kinase inhibitors in rheumatoid arthritis

patients who are insufficient responders to conventional anti-rheumatic drugs. Drugs. 2024;84(8):877-94.
7. Molteni E, Adinolfi A, Bondi V, Delvino P, Sakellariou G, Trentanni C, et al. Novel insights into the management of rheumatoid arthritis: one year in review 2024. Clin Exp Rheumatol. 2024;42(5):947-60.
8. Soriano ER, Mysler E, Rios C, Xavier RM, Cardiel MH, Citera G. Rheumatoid arthritis in Latin America: pharmacotherapy and clinical challenges. Expert Opinion on Pharmacotherapy. 2024;25(15):2023-33.
9. Kakkadath M, Naidu D, Kanthlal S, Sharun K. Combating Methotrexate Resistance in Cancer Treatment: A Review on Navigating Pathways and Enhancing Its Efficacy With Fat-Soluble Vitamins. Scientifica. 2025;2025(1):8259470.
10. Martinez-Molina C, Gich I, Diaz-Torné C, Park HS, Feliu A, Vidal S, et al. Patient-related factors influencing the effectiveness and safety of Janus Kinase inhibitors in rheumatoid arthritis: A real-world study. Scientific reports. 2024;14(1):172.
11. Andreoli L, Guadagni I, Picarelli G, Principi M. Comprehensive reproductive healthcare for women with immune-mediated inflammatory diseases: Addressing rheumatoid arthritis, spondyloarthritis and inflammatory bowel disease through life's stages. Autoimmunity Reviews. 2024;23(3):103507.
12. Gao Y, Zhang Y, Liu X. Rheumatoid arthritis: pathogenesis and therapeutic advances. MedComm. 2024;5(3):e509.
13. Prajapati P, Singh P, Doshi G. Emerging Therapeutic Targets in Rheumatoid Arthritis: Focusing on HIF-1α, Nrf2, STATs, and RORγt. Current Drug Targets. 2025.
14. Xia X, He C, Xue Z, Wang Y, Qin Y, Ren Z, et al. Single-cell immunoprofile of synovial fluid in rheumatoid arthritis with TNF/JAK inhibitor treatment. Nature Communications. 2025;16(1):2152.
15. Peterson D, Damsky W, King B. JAK Inhibitors as Immunomodulators. Immunomodulators and Biologics in Dermatologic Treatment: Turning Theory into Practice: Springer; 2024. p. 57-71.
16. Faris A, Cacciatore I, Alnajjar R, Aouidate A, Al Mughram MH, Elhallaoui M. Computational insights into rational design and virtual screening of pyrazolopyrimidine derivatives targeting Janus kinase 3 (JAK3). Frontiers in Chemistry. 2024;12:1425220.
17. MEYERS AF, Fleming C. New Drugs for Rheumatism: The Present and Future of Rheumatism Therapy. 2024.
18. Huang Y, Xiong Z, Liao S, Li F, Wu L. Novel Targets for Chronic Inflammatory Diseases: Focus on Therapeutic Drugs and Natural Compounds, volume II: Frontiers Media SA; 2024.
19. Ageeva T, Rizvanov A, Mukhamedshina Y. NF-κB and JAK/STAT signaling pathways as crucial regulators of neuroinflammation and astrocyte modulation in spinal cord injury. Cells. 2024;13(7):581.
20. Parveen S, Fatma M, Mir SS, Dermime S, Uddin S. JAK-STAT Signaling in Autoimmunity and Cancer. ImmunoTargets and Therapy. 2025:523-54.
21. Dandash F, Salhab Z, Issa R, Al Dirani Z, Hamze M, Fares G, et al. Targeting the double-edged sword: cytokines in the pathogenesis and treatment of autoimmune diseases. Inflammopharmacology. 2025:1-23.
22. Jain A, Bishnoi M, Prajapati SK, Acharya S, Kapre S, Singhvi G, et al. Targeting rheumatoid arthritis: a molecular perspective on biologic therapies and clinical progress. Journal of Biological Engineering. 2025;19(1):67.
23. Li Z, Liu H, Xie Q, Yin G. Macrophage involvement in idiopathic inflammatory myopathy: pathogenic mechanisms and therapeutic prospects. Journal of Inflammation. 2024;21(1):48.
24. Priya S, Jain KK, Daryani J, Desai VM, Kathuria H, Singhvi G. Revolutionizing rheumatoid arthritis treatment with emerging cutaneous drug delivery systems: overcoming the challenges and paving the way forward. Nanoscale. 2025;17(1):65-87.
25. Alarcon JF, Karusan NR, Presciutti C, Miras J, Magana JR, Guerra-Rebollo M, et al. Revolutionizing rheumatoid arthritis therapy: the potential of lipid nanocarriers. RSC advances. 2025;15(33):27388-402.
26. Li J, Li W, Zhuang L. Natural biomimetic nano-system for drug delivery in the treatment of rheumatoid arthritis: A literature review of the last 5 years. Frontiers in Medicine. 2024;11:1385123.
27. Sharma S, Ghosh R, Marianesan AB, Hussain S, Pandey JD, Kumar M. Nanostructured lipid carriers in Rheumatoid Arthritis: treatment, advancements and applications. Inflammopharmacology. 2025:1-18.
28. Wang W, Wang Z, Ling A, Zhang C, Lv M, Huang L, et al. Research progress in the treatment of rheumatoid arthritis with Sinomenine and related

formulations based on different administration routes. Frontiers in Pharmacology. 2025;16:1613679.
29. Peng Y, Yang Z, Li J, Liu S. Research progress on nanotechnology of traditional Chinese medicine to enhance the therapeutic effect of osteoarthritis. Drug Delivery and Translational Research. 2024;14(6):1517-34.
30. Chung Y-K, Hsu C-Y, Wang Y-T, Tran TTP, Alalaiwe A, Fang J-Y. Nanocarrier-enabled delivery of natural anti-obesity agents. Nanomedicine. 2025:1-21.
31. Mahajan A, Sharma G, Thakur A, Singh B, Mehta H, Mittal N, et al. Tofacitinib in dermatology: a potential opportunity for topical applicability through novel drug-delivery systems. Nanomedicine. 2024;19(1):79-101.
32. Nguyen T-T-L, Duong V-A. A Review on Nanosystem-Based Delivery of Tofacitinib for Enhanced Treatment of Autoimmune Diseases and Inflammation. BioNanoScience. 2024;14(2):2048-64.
33. Li Y, Cheng Y, Cai Y, Duan Z, Xu H, Huang Y, et al. Novel Small-Molecule Treatment and Emerging Biological Therapy for Psoriasis. Biomedicines. 2025;13(4):781.
34. Tabassum S, Makula A. Tofacitinib citrate delivery through pharmaceutical formulations for divergent therapeutic treatments. Journal of Advanced Scientific Research. 2024;15(1):1-8.
35. Nikolova-Ganeva KA, Mihaylova NM, Kechidzhieva LA, Ivanova KI, Zarkov AS, Parzhanov DL, et al. The Therapeutic Potential of Phytochemicals Unlocks New Avenues in the Management of Rheumatoid Arthritis. International Journal of Molecular Sciences. 2025;26(14):6813.
36. Xu L, Shao Z, Fang X, Xin Z, Zhao S, Zhang H, et al., editors. Exploring precision treatments in immune-mediated inflammatory diseases: Harnessing the infinite potential of nucleic acid delivery. Exploration; 2025: Wiley Online Library.
37. LATEEF DA, AJEED AM, MAHMEED BAH. THE ROLE OF OMEGA-3 FATTY ACIDS AND VITAMIN D IN THE PREVENTION AND MANAGEMENT OF RHEUMATIC DISEASES. cytokines.1:2.
38. Liu J. Prostaglandins and other lipids as therapeutic targets and prognostic biomarkers in rheumatoid arthritis. Karolinska Institutet Solna; 2025.
39. Yuan J, Li X, Jia Y, Zhang H. Anti-TNFa in inflammatory bowel disease: from originators to. Biologic Drugs in Immune-Mediated Inflammatory Diseases: Validation, Drug-Utilization, Effectiveness, Regulation, Costs, and Safety in the Real World. 2025:66.
40. Gladman D, Walsh J, Merola J, Ritchlin C, Tanaka Y, Favalli E, et al., editors. Bimekizumab Maintained Efficacy Responses in Patients with Active Psoriatic Arthritis: Up to 2-Year Results from Two Phase 3 Studies. The Journal of Rheumatology; 2025: The Journal of Rheumatology.
41. Needham A, Tan J, Cheng V, De Vera M, Amiri N, editors. Janus Kinase Inhibitor Exposure During Pregnancy in Immune-Mediated Inflammatory Diseases: A Case Series of 3 Patients. The Journal of Rheumatology; 2025: The Journal of Rheumatology.
42. Youssef E, Weddle K, Zimmerman L, Palmer D. Pharmacovigilance in Cell and Gene Therapy: Evolving Challenges in Risk Management and Long-Term Follow-Up: E. Youssef et al. Drug Safety. 2025:1-27.
43. Steiner T, Purrucker JC, Aguiar de Sousa D, Apostolaki-Hansson T, Beck J, Christensen H, et al. European Stroke Organisation (ESO) and European Association of Neurosurgical Societies (EANS) guideline on stroke due to spontaneous intracerebral haemorrhage. European Stroke Journal. 2025:23969873251340815.
44. Gandy C, Bazzazzadehgan S, Bruera S, Huang Y. Evaluation of Real-World Evidence to Assess Effectiveness Outcomes of Janus Kinase Inhibitors for Rheumatoid Arthritis: A Systematic Review of US Studies. Drug, Healthcare, and Patient Safety. 2025:25-49.
45. El Ouardi N, Hmamouchi I, Abouqal R, Allali F, Bahiri R, El Bouchti I, et al. Real-world evidence of biological treatments in rheumatoid arthritis and spondyloarthritis in Morocco: results of the RBSMR registry. BMC Rheumatology. 2025;9(1):62.
46. Nascimento MMP, Azuelos A, Nóbrega ILP, Pitombeira MS, Martinez ATA, de Carvalho JF, et al. State of the Art in Novel Treatment Strategies in Rheumatoid Arthritis: A Brief Review. Mediterranean Journal of Rheumatology. 2025;36(2):149.
47. G DB, Jyotsna O, Kumar US, M AS, Sham S, N MA. A Consensus Report by the RAPID-India Group on Optimising Tofacitinib Treatment for Indian Patients with Rheumatoid Arthritis, Axial Spondyloarthritis and Psoriatic Arthritis. Indian Journal of Rheumatology 09733698251316342.
48. Kerschbaumer A, Steiner M, Pruckner P, Wildner B, Maad M, Smolen JS, et al. Global recruitment patterns and placebo responses in clinical

trials of rheumatoid arthritis. Annals of the Rheumatic Diseases. 2025.
49. Yiu CH, Ianni BD, Day RO, Raubenheimer J, Lu CY. Treatment Persistence in Rheumatoid Arthritis Before and After Etanercept Biosimilar Introduction: A Nationwide Australian Real-World Study. Pharmaceutical Medicine. 2025:1-13.
50. Pandita D, Altekar S, Vapiwala F. Are we willing to embrace the future? The need to move towards sustainable mobility. Discover Sustainability. 2025;6(1):431.
51. Calcini G, Bolcato V, Tronconi LP, Basile G. Efficacy and Clinical Application of Physical Activity in Substance Use Disorder Rehabilitation: A Review on Mechanism and Benefits. Physiologia. 2025;5(1):7.
52. Puccini A, Viscardi G, Ciani O, Efficace F, Piattelli A, Beretta GD, et al. Patient-reported outcomes (PROs) in clinical trials and in clinical practice: report from the XXI national conference of the Italian Association of Medical Oncology (AIOM). BMJ Oncology. 2025;4(1):e000783.
53. Bento AR, Duque AR, Gonçalves N, Vaz P, Calção S, Benedito V, et al. Interventions by Rehabilitation Nurse Specialists in the Training of Informal Carers of Older People at Home with Chronic Diseases: A Scoping Review. International Journal of Environmental Research and Public Health. 2025;22(7):971.
54. Roy A, Kumar A, Srivastava AK, Ansari F, Kumar K, Vishwakarma M, et al. Disparities in Access to Essential Medicines in India: A Systematic Review of Availability, Affordability and Policy Challenges. International Journal of Scientific Research and Technology. 2025.
55. Nash P, Kerschbaumer A, Konzett V, Aletaha D, Dörner T, Fleischmann R, et al. Expert consensus statement on the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: 2024 update. Annals of the rheumatic diseases. 2025;84(5):664-79.
56. Torres Zambrano G, Uría Gonzalez Tova J, Peramo Moyaa B, Gayáy MR, Ahamed FM. Stem Cells for Urogynecological Diseases: IGI Global; 2025.
57. Weathers Jr, MD. Exploring the Reentry Experiences of Black Returning Citizens With Disabilities: An Interpretative Phenomenological Analysis: The University of Wisconsin-Madison; 2025.
58. Makwero MT, Muula AS, Anyanwu FC, Maposa I, Igumbor J. Perception of patient-centred care and its relationship with management outcomes and complications among patients with DM in Malawi. BMJ Open. 2025;15(7):e090308.
59. Nyberg L, Halfvarson J, Söderling J, Olén O, Strid H, Hedin CR, et al. Prospective observational study of tofacitinib in ulcerative colitis–analysis of clinical data, fatigue, and health-related quality of life during the induction phase. Therapeutic Advances in Gastroenterology. 2025;18:17562848251343427.
60. Gleeson D, Chapman S, McAteer H, Qin A, Gregory J, Pizzato J, et al. Janus kinase inhibitors in palmoplantar pustulosis: a mixed-methods feasibility (JAKPPPOT) trial protocol. BMJ Open. 2025;15(8):e106361.
61. Zehrer A, Rausch A, Jordan PM, Werz O, Tom Dieck H, Berngruber T. Enhancing tofacitinib's therapeutic efficacy in murine arthritis with a synbiotic formulation comprising Bacillus megaterium DSM 32963 and an Omega-3 fatty acid lysine salt. Frontiers in Immunology. 2025;16:1540878.
62. Yang H, Wang S, Zhou Q, Geng P, Lu Z, Lin Q, et al. Assessments of CYP-Inhibition-Based Drug–Drug Interactions Between Tofacitinib and Lipid-Lowering Agents in Rats, Both In Vitro and In Vivo. Pharmacology Research & Perspectives. 2025;13(3):e70127.
63. Baciu T, Neagu AE, Saulescu IC, Opris-Belinski D. Unveiling Sex-Related Variability in Psoriatic Arthritis: A Call for Personalized Care. Journal of Clinical Medicine. 2025;14(12):4124.
64. Parvin N, Joo SW, Mandal TK. Biodegradable and stimuli-responsive nanomaterials for targeted drug delivery in autoimmune diseases. Journal of Functional Biomaterials. 2025;16(1):24.
65. Pannu S, Pal R, Verma I. Exploring the Therapeutic Potential of Nanocarrier-Mediated Drug Delivery in Rheumatoid Arthritis (RA) Treatment. Current Rheumatology Reviews. 2025.
66. Song M-H, Yan Y, Chen B, Gong L, Chen L, Feng J, et al. Advances in Intra-Articular Injection Hydrogel Drug Delivery Systems in the Treatment of Rheumatoid Arthritis. Pharmaceutics. 2025;17(9):1118.
67. Raj A, Rahul K, Chandran CS, Alex AT. 15 Future Prospects of Synthetic Polymers in Drug Delivery. Synthetic Polymeric Materials-Based Drug Delivery Systems for Inflammatory Diseases. 2025;25:212.
68. Yao Q, Chen X, Sheng H, Zhang Y, Chen R, Fan P, et al. Lubricating nano/micro particles for osteoarthritis therapy. Materials Horizons. 2025.

69. Back W, Park J-H. Hydrogel-Based Strategies for Managing Rheumatoid Arthritis: From Sustained Drug Release to Cell-Based Therapies. ACS Biomaterials Science & Engineering. 2025.
70. Hussain FH, Mahmad S, Yousuf MA, Virendra K, Atik S. Frontiers in Nanotechnology for Targeted Drug Delivery: Stimuli-Responsive Systems and Brain-Targeting Nanocarriers.
71. Wu Q-X, De Isla N, Zhang L. Biomaterial-Based Nucleic Acid Delivery Systems for In Situ Tissue Engineering and Regenerative Medicine. International Journal of Molecular Sciences. 2025;26(15):7384.