South American Publishing

SAP Rehabilitation and Sports Medicine. 2025;5:123
doi: 10.62486/rsm2025123

REVIEW

Rheumatoid arthritis: Strategies to combat pain in patients refractory to conventional treatments who cannot access medication with biological drugs

Artritis reumatoidea: Estrategias para combatir el dolor en pacientes refractarios a los tratamientos convencionales que no pueden acceder a la medicación con fármacos biológicos

Pedro Sebastián Rodriguez[1]
Fátima Bergalli[1]

[1] Universidad Abierta Interamericana, Facultad de Medicina y Ciencias de la Salud. Buenos Aires, Argentina.

Submitted: 14-05-2025 | Revised: 30-07-2025 | Accepted: 30-08-2025 | Published: 02-09-2025

ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease with multi-organ involvement. It primarily affects peripheral joints symmetrically. While its pathophysiology is largely understood, its etiology remains unknown. Cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-6 play a crucial role in the pathogenesis and perpetuation of inflammation in RA. The natural progression of RA leads to joint deformity and disability, as well as a reduced life expectancy due to increased cardiovascular risk, pulmonary involvement, infections, iatrogenic causes, or tumors. Chronic non-cancer pain, joint deformity, and fatigue are the cardinal symptoms of RA. Early diagnosis and access to targeted therapies aimed at early remission have improved the prognosis of rheumatoid arthritis (RA). The latest generation of treatments, known as DMARDs (dsDMARDs), are expensive and practically inaccessible to RA patients. Therefore, alternative treatments for RA must be considered when DMARDs prove refractory for these patients. Materials and methods: This systematic review consists of a literature analysis on RA, with the main objective of identifying conventional and alternative treatments within the context of the disease. Searches were conducted in the following online databases: Cochrane Library, Google Scholar, and SciELO. Results: A total of 296 articles were obtained that refer to the subject of study and its definitions. Conclusion: To publicize and encompass all existing treatment options for patients diagnosed with RA, promoting access to comprehensive literature resulting from thorough research that contributes to improving the quality of life of these patients.

Keywords: Rheumatoid arthritis, pathophysiology, symptoms, treatment, cost analysis, adjuvants in symptomatic relief in patients with RA.

RESUMEN

La artritis reumatoide (AR) es una enfermedad inflamatoria crónica autoinmune con afectación multiorganica. Daña principalmente a las articulaciones periféricas de forma simétrica. La fisiopatología se ha logrado comprender en gran medida pero su etiología sigue siendo aún desconocida. Las citosinas como el factor de necrosis tumoral (TNF) y la interleucina (IL)-6, juegan un rol importantísimo en la patogénesis y la perpetuación de la inflamación en la AR. La evolución natural de la AR causa deformidad articular y discapacidad, además de una reducción de la esperanza de vida, por aumento del riesgo cardiovascular, afectación pulmonar, infecciones, iatrogenia o tumores. El dolor crónico no oncológico, la deformidad articular y la fatiga son los síntomas cardinales de la AR. El diagnóstico precoz y la posibilidad de acceso a la administración de fármacos dirigidos que buscan la remisión temprana de la enfermedad han mejorado el pronóstico de la AR. El tratamiento propuesto de última generación se denomina FAMEsd, son de costo elevado e inaccesible prácticamente para los pacientes con AR. Esto hace que se deban tener presentes tratamientos alternativos a la AR cuando los tratamientos con FAME resultan refractarios para estos pacientes. Material y métodos: esta revisión sistemática consiste en un análisis de bibliográfico sobre la AR y su objetivo principal precisar en el contexto de enfermedad tratamientos convencionales y alternativos. Las búsquedas se realizaron en las bases de datos disponibles en internet: Cochrane Library, Google Académico, SciELO. Resultados: Se obtuvieron un total de 296 artículos que hacen referencia al objeto de estudio y sus definiciones. Conclusión: Dar a conocer y englobar todas las posibilidades de tratamientos existentes para los pacientes con diagnostico de AR promoviendo que las personas accedan a una literatura completa producto de una investigación exhaustiva que contribuya con la oportunidad de mejorar la calidad de vida de estos pacientes.

Palabras clave: Artritis reumatoidea, fisiopatología, síntomas, tratamiento, análisis de costos,coadyuvantes en el alivio sintomático en pacientes con AR.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of autoimmune origin that can affect many tissues and organs but primarily the joints, causing nonsuppurative inflammatory and proliferative synovitis. In many patients, RA progresses to destruction of the articular cartilage and joint ankylosis. Extra-articular lesions can affect the skin, blood vessels, heart, and lungs; therefore, clinical manifestations may resemble those of other systemic autoimmune diseases, such as systemic lupus erythematosus or scleroderma. Rheumatoid arthritis is an autoimmune disease with a global incidence of approximately 1%1 ; its incidence increases between the second and fourth decades of life, and it is three times more common in women than in men.2

Genetic predisposition and environmental factors contribute to the onset, progression, and chronicity of the disease. As with other autoimmune diseases, pathological changes are caused by antibodies against autoantigens and by inflammation triggered by cytokines, which are secreted primarily by CD4+ T lymphocytes2.

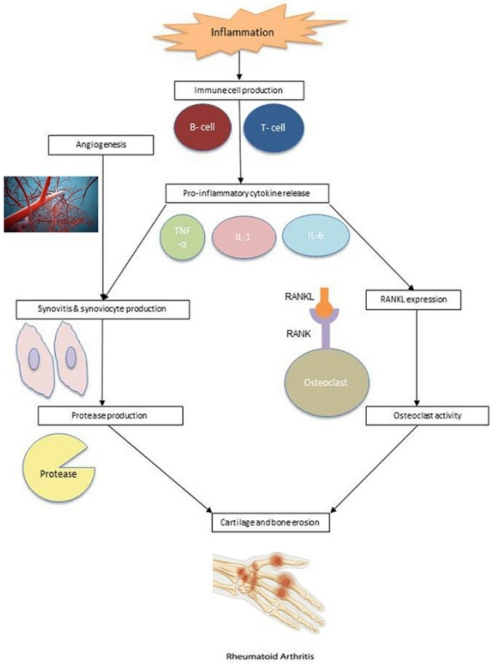


FIG 3. FLOWCHART.

CD4+ helper T cells produce cytokines that stimulate inflammatory cells to cause tissue damage. In inflamed joints, cytokines such as IFN-□ from CD4+ helper T cells are expressed; these cytokines activate macrophages and synovial cells present in the joint; IL-7 from CD4+ helper T cells attracts neutrophils and monocytes; and TNF-□ and IL-1 from macrophages stimulate synovial cells present in the affected joint to secrete proteases that destroy hyaline cartilage; and RANKL is expressed by activated T cells, which stimulates bone resorption (see Figure 2). The synovium in RA contains germinal centers with secondary follicles and numerous plasma cells that produce antibodies, some of which are directed against autoantigens. Many antibodies produced in lymphoid organs and in the synovium are specific for citrullinated peptides (CCPs), in which arginine residues are converted to citrulline posttranslationally. In RA, antigen–antibody complexes containing citrullinated fibrinogen, type II collagen, □-enolase, and vimentin are deposited in the joints. Antibodies against these peptides are diagnostic markers of the disease and may be involved in joint damage. These data indicate that elevated anti-CCP levels, combined with T-cell responses to citrullinated proteins, contribute to the chronicity of the disease (2).

The histological findings in arthritic lesions include synovial cell hyperplasia and proliferation; dense inflammatory infiltrates consisting of CD4-positive helper T-cell follicles, plasma cells, dendritic cells, and macrophages; increased vascularization due to angiogenesis; fibrinopurulent exudate on the synovial membrane and articular surfaces; and osteoclastic activity in the underlying bone, allowing the synovial membrane to penetrate the bone and cause juxta-articular erosions and subchondral cysts. Together, these changes result in the formation of a synovial pannus, a mass of edematous synovium, inflammatory cells, granulation tissue, and fibroblasts that grow over the articular cartilage and erode it. The clinical presentation has a slow and gradual onset, with general malaise, fatigue, and musculoskeletal pain. After weeks or months, it affects the joints, first the small ones and then the large ones, with manifestations beginning in the hands (metacarpophalangeal and proximal interphalangeal joints) and feet, followed by the wrists, elbows, and knees. These patients present with swollen, warm, painful, and stiff joints in the morning and after periods of inactivity (3).

RA is associated with inflammation of tendons, ligaments, and adjacent skeletal muscles, leading to radial deviation of the wrist and ulnar deviation of the fingers with swan neck or buttonhole deformities, ultimately resulting in an unstable joint with a limited range of motion. The most common symptoms observed are joint pain and swelling, morning stiffness in the affected joint lasting more than 30 minutes, fatigue, low-grade fever, loss of appetite, and symmetrical involvement (e.g., both wrists or knees) 4.

Treatment for RA is based on patient education, physical and occupational therapy, and the use of medications (5).

The main extra-articular manifestations of rheumatoid arthritis are as follows: 1) Skin: rheumatoid subcutaneous nodules. In 25% of cases, these affect skin areas subject to pressure, such as the cubital region of the forearm, elbows, occiput, and lumbosacral region. 2) Blood vessels: individuals with advanced disease, nodules, and high RF titers are at high risk of developing vasculitis. 3) The pericardium, lungs, and pleura may become fibrotic. 4) Leukocytoclastic vasculitis causes purpura, skin ulcers, and nail bed infarcts. 5) Uveitis and keratoconjunctivitis2.

Currently, a wide range of therapeutic options are available, and treatment focuses on a stepwise and personalized approach; the drugs used to treat RA are divided into three classes: nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and FAME, which include FAMEsc, FAMEb, and FAMEsd. These last two groups of FAME are identified under the term "-targeted therapy".

Biological therapy has revolutionized the treatment of RA; these molecules target specific proinflammatory cytokines and have proven more effective than traditional FAME, achieving disease remission in a greater number of patients. In general, these are antibodies (human or chimeric) or fusion proteins with specific effects on a target, promoting the blocking of a molecule, its receptor, or the lysis of a cell subpopulation (21). One of the most notable characteristics of biologic therapies is their rapid onset of action compared with traditional DMARDs. Currently, nine marketed biologics are available. All have been shown to be effective compared with placebo, but there are no direct comparisons between them, nor is there sufficient information on their long-term safety. We can classify biologic drugs for treating RA into 5 groups on the basis of their mechanism of action: 1. Anti-TNF-alpha antibodies: infliximab (INF), etanercept (ETN), adalimumab, golimumab (GOL), and certolizumab (CTZ). 2. IL-1 antagonist: anakinra (ANK). 3. Anti-CD20 monoclonal antibody: RTX. 4. T-cell activity-modulating fusion protein: abatacept (ABT). 5. IL-6 antagonist: tocilizumab (TCZ)5. These drugs act on specific components of the immune system and are generally more effective than traditional treatments but also much more expensive. The economic evaluation of these medications includes the following: 1) Direct costs: drug price, medical consultations, and laboratory tests. 2) Indirect costs: loss of work productivity, absenteeism, and disability. 3) Intangible costs: impact on the patient's quality of life. In addition to cost calculations, other tools, such as cost-effectiveness and cost-utility analysis, are used to determine whether the clinical benefit justifies the expense. There are also barriers to affordable access to these medications, such as the following: a) High price: biologics are often very expensive, which limits their availability in public and private healthcare systems. b) Geographic inequality: Access varies by country, insurance coverage, and healthcare infrastructure. c) Intellectual property: Patents limit the entry of more affordable biosimilars. Owing to the high cost of the drugs in this therapeutic class, the implementation of public policies to promote public production and the use of biosimilars is recommended.7

Rheumatoid arthritis and pain

The main types of pain are as follows: 1) nociceptive pain, which is caused by tissue damage (such as to muscles or joints); this is the typical pain associated with injury or inflammation; and 2) neuropathic pain, which is caused by damage or dysfunction in the nervous system; it can feel like it is burning, tingling, or electric shocks and is associated with changes in sensitivity, such as allodynia, hyperalgesia, and/or paresthesia. 3) Nociplastic pain, in which the nervous system is capable of altering how it perceives pain without necessarily involving tissue damage. In rheumatoid arthritis, pain is persistent (i.e., chronic pain—lasting more than 3 months) and combines neuropathic, nociceptive, and nociceptive pain; the recommended management involves the use of pharmacological treatments with analgesics and adjuvants. Additionally, nonpharmacological therapies such as physical therapy, cognitive–behavioral therapy, physical exercise, education, and self-care are always key to improving patient autonomy, and the use of adjunctive medication in the treatment of rheumatoid arthritis pain is a promising strategy. Adjuvants are drugs that were not originally designed as analgesics but help enhance the effect of pain treatment. They are used especially when pain is difficult to control with traditional analgesics alone. They work primarily by modulating pain perception in the central and peripheral nervous systems; improving associated symptoms such as anxiety, insomnia, or muscle spasms; and allowing for a reduction in the dose of opioids or NSAIDs, thereby reducing adverse effects. The main types of adjuvants are as follows:

1) Antidepressants such as amitriptyline, duloxetine, and desvenlafaxine; 2) anticonvulsants such as gabapentin and pregabalin; 3) muscle relaxants such as cyclobenzaprine, baclofen, and ; and 3) local anesthetics such as lidocaine and bupivacaine in infiltrations or compounded preparations. The decision to treat a patient diagnosed with rheumatoid arthritis with adjunctive medication must be made with caution, and healthcare professionals must be able to identify the predominant pain and use rational polypharmacy (low doses of different medications with distinct kinetics and dynamics to enhance action through multiple pathways and reduce the risk of adverse effects) as a therapeutic alternative for patients refractory to conventional treatments and unable to access FAME9.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that severely compromises the quality of life of those who suffer from it. Although disease-modifying antirheumatic drugs (DMARDs) constitute the cornerstone of treatment, a significant proportion of patients develop therapeutic resistance, resulting in a refractory clinical profile. While biologic therapies represent effective alternatives, access to them remains limited by economic, social, and structural factors within the healthcare system.10

Given this scenario, adjunctive treatments—both pharmacological and nonpharmacological—play a fundamental role in the comprehensive management of RA. On the pharmacological front, the use of analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), controlled-dose corticosteroids, and other agents, such as antidepressants, allows for optimized pain control and improved functionality, especially in patients excluded from biologic therapies; efforts are also being made to promote the development of comprehensive care models, generate scientific evidence regarding their efficacy, and contribute to the formulation of public policies that ensure equitable access to these therapeutic interventions.11,12

The theoretical foundation of this research was based on a multidisciplinary and comprehensive approach to the treatment of RA, recognizing that pain is not only a physical phenomenon but also an emotional and social phenomenon. Therefore, the aim was to investigate and systematize these strategies as viable and accessible alternatives for patients who cannot access biologic therapies.

To develop the research protocol and subsequently conduct the systematic review, a literature search was performed on the basis of recommendations from experts in the field.

Databases such as PubMed, Google Scholar, TripDataBase, and SciELO were used to review the texts. Systematic review articles, case series reports, and journal and newspaper articles published in English and Spanish were studied. No filters were applied on the basis of publication date.

The Medical Subject Headings (MeSH) terms and the Boolean operator AND were used: (“rheumatoid arthritis”[MeSH]”), (“rheumatoid arthritis”[MeSH]) AND “rheumatoid arthritis/epidemiology”[MeSH], “rheumatoid arthritis/physiopathology”[MeSH], (“rheumatoid arthritis”[MeSH]) AND “conventional treatment”[Mesh], (“rheumatoid arthritis”[Mesh]) AND “biological drugs”[Mesh], (“rheumatoid arthritis”[Mesh]) AND “alternative treatments” [Mesh], (“pain”[Mesh]) AND “rheumatoid arthritis”[Mesh], (“Pain”[Mesh]) AND “Adjuvant medication”[Mesh].

The relevant information was saved on the Zotero platform (bibliographic reference manager), which is available for Windows. The articles were organized into different folders to keep the data grouped and optimize the reading time for each topic, facilitating the subsequent task of final article selection.

All titles were reviewed, but only those relevant to the research topic were considered. The abstracts and full-text articles were subsequently read.

The selected information was based on the general aspects of the topic and the PICO framework (an acronym for population, intervention, comparison, and outcomes). The research was conducted by analyzing the relevant notes extracted from the selected articles.

Within the MeSH term "rheumatoid arthritis," articles were analyzed by topic: definition, etiology, epidemiology, physiology, pathophysiology, diagnosis, and treatment.

A total of 296 texts were shortlisted, from which 61 were selected for data collection and to address the research question. (See Flowchart – Fig. 3)

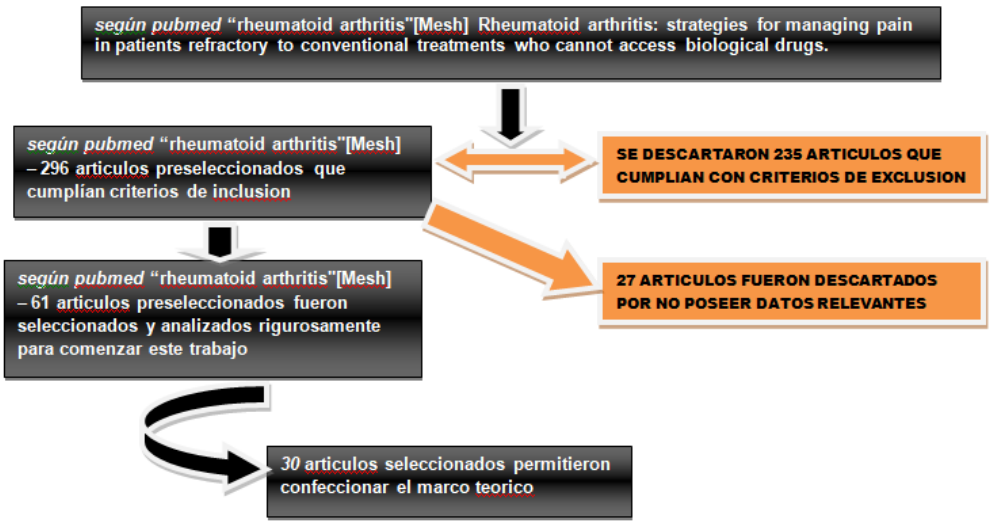


Fig. 4. Comparison of efficacy, safety, and cost-effectiveness for rheumatoid arthritis. Author's own work.

AUTHOR'S OWN

This critical analysis focused on the scientific literature mentioned above regarding pharmacological strategies used for pain management in patients with rheumatoid arthritis refractory to conventional treatments who do not have access to biologic therapies. The analysis followed specific parameters to achieve specific objectives, such as identifying the main adjunctive pharmacological agents used in pain management in patients with rheumatoid arthritis, such as NSAIDs, corticosteroids, antidepressants, anticonvulsants, and low-potency opioids; evaluating the reported clinical efficacy of these drugs in reducing pain, improving function, and enhancing quality of life in patients with refractory RA; analyzing the mechanisms of action of adjunctive drugs in the context of nociceptive and neuropathic inflammatory pain associated with RA; identifying the main pharmacological strategies described in the literature for pain management in patients with rheumatoid arthritis; and examining the economic, social, and healthcare barriers that limit access to biologic treatments, as reported in scientific studies.

From the above, the following research question emerged: What are the current strategies that can be used in patients who are refractory to conventional treatment for rheumatoid arthritis and who cannot access treatment with biologics?

To develop the research protocol and conduct the systematic review, a literature search was performed under the professional guidance of the supervisor, applying the methodology acquired in the university academic setting.

In preparing the scientific article, sources from various databases were consulted, including systematic reviews, systematic reviews of data analyses, case reports, journal articles, and open-access publications.

The following Medical Subject Headings (MeSH) terms and the Boolean operator AND were used: ("rheumatoid arthritis"[Mesh"[Mesh]) AND "rheumatoid arthritis"[Mesh]) AND "rheumatoid arthritis/epidemiology"[Mesh], "rheumatoid arthritis/physiopathology"[Mesh], ("rheumatoid arthritis"[Mesh]) AND "conventional treatment"[Mesh], ("rheumatoid arthritis"[Mesh]) AND "biological drugs"[Mesh], ("rheumatoid arthritis"[Mesh]) AND "alternative treatments" [Mesh], ("pain"[Mesh]) AND "rheumatoid arthritis"[Mesh], ("Pain"[Mesh]) AND "Adjuvant medication"[Mesh].

The relevant information was stored in Zotero, a bibliographic reference manager compatible with Windows. On this platform, the articles were organized and numbered within different folders, which allowed the data to be classified by topic, streamlined the reading process, and facilitated the final document selection process.

The most relevant data were recorded in a text file created in Microsoft Word and presented in the form of annotations for proper preservation.

The progress and development of the research were based on relevant annotations obtained from the previously selected articles. A total of 296 articles related to the topic were analyzed, and 61 were initially selected. Most were discarded because they contained insufficient information to yield meaningful results. Finally, articles were highlighted, 30 of which proved essential for developing the theoretical framework and justification in the previous step (research protocol). These 30 articles provided important information that allowed for the establishment of an integrative concept and supported the development of the theoretical framework, data analysis, and corresponding discussion.

The central focus of this systematic review was to clearly define the scope of the study, whose primary objective was to critically analyze the available scientific literature on pharmacological strategies used for pain management in patients with rheumatoid arthritis who are refractory to conventional treatments and do not have access to biologic therapies. Specific objectives were also considered, such as identifying the main adjunctive pharmacological agents used in pain management in patients with rheumatoid arthritis (NSAIDs, corticosteroids, tricyclic antidepressants, anticonvulsants, and low-potency opioids); evaluating the reported clinical efficacy of these drugs in reducing pain, improving function, and enhancing quality of life in patients with refractory RA; analyzing the mechanisms of action of adjunctive drugs in the context of inflammatory and nociceptive pain associated with RA; identifying the main pharmacological strategies described in the literature for pain management in patients with rheumatoid arthritis; and examining the economic, social, and healthcare barriers that limit access to biologic treatments, as reported in scientific studies.

The research question posed was therefore as follows:

Q: Scientific articles mentioning patients who are diagnosed with rheumatoid arthritis, who do not respond to conventional therapies and who cannot access biologic drugs.

I: To identify therapeutic alternatives for these patients in the published texts.

C: No.

O: To compile data that allow healthcare professionals rapid access to therapeutic alternatives in the event that they must treat a patient diagnosed with rheumatoid arthritis who has used conventional drugs (and who was refractory or experienced adverse effects) and who cannot access biologic medication.

METHODS

With respect to the research methodology, the study on the topic was conducted following the guidelines acquired in medical school courses, literature review, and the final thesis. This process enabled the development of a systematic literature review with a critical, descriptive, and evidence-based perspective aimed at generating solid evidence regarding rheumatoid arthritis and strategies designed to alleviate pain in patients refractory to conventional treatments who lack access to biologic therapies.

The study population comprised scientific articles that met the inclusion criteria: patients with a confirmed diagnosis of rheumatoid arthritis or who were refractory to conventional DMARDs and who did not receive biological treatment for economic, administrative, or availability reasons.

The inclusion criteria used for the articles were as follows: articles published in scientific journals that addressed the use of adjunctive medications (analgesics, NSAIDs, corticosteroids, antidepressants, anticonvulsants, low-potency opioids, etc.) for the management of nociceptive and neuropathic inflammatory pain in patients with refractory rheumatoid arthritis; studies including patients with a confirmed diagnosis of rheumatoid arthritis according to the ACR/EULAR classification criteria, who do not respond adequately to conventional DMARDs such as methotrexate, leflunomide, or sulfasalazine; research reporting clinical outcomes related to the efficacy, safety, and accessibility of adjunctive pharmacological treatments in this population; and studies analyzing the impact of economic, social, or administrative barriers on access to biologic therapies and justifying the use of complementary pharmacological alternatives.

The exclusion criteria were articles on patients receiving biological therapy at the time of the study; publications containing diagnostic information on concomitant rheumatic diseases (such as lupus or spondyloarthritis); studies of patients treated with biological medications; literature analyzing other concomitant rheumatic diseases; and articles that did not mention pain, functionality, or quality of life.

The following guidelines were used for data collection: a literature search on scientific platforms available online using MeSH terms (Medical Subject Headings) and the Boolean operator AND: ("rheumatoid arthritis"[Mesh],"rheumatoid arthritis"[Mesh]) AND "rheumatoid arthritis/epidemiology"[Mesh], "rheumatoid arthritis"[Mesh]) AND "conventional treatment"[Mesh], ("rheumatoid arthritis"[Mesh]) AND "biological drugs"[Mesh], ("rheumatoid arthritis"[Mesh]) AND "MES"[Mesh], ("rheumatoid arthritis"[Mesh]) AND "alternative treatments" [Mesh], ("pain"[Mesh]) AND " rheumatoid arthritis"[Mesh], ("Pain"[Mesh]) AND " Adjuvant medication "[Mesh]; an initial evaluation of the articles on the topic to be analyzed was conducted; an assessment of the implementation of pharmacological strategies was performed; and finally, follow-up and a final evaluation were carried out using the same instruments.

The study was conducted in an academic setting as part of the final thesis for the medical degree program at the Inter-American Open University.

The selected variables and their operational definitions are described below:

The following definitions were taken into account in the preparation of Table 1: (a) Pain was measured quantitatively using the visual analog scale (VAS), which allows for the assessment of the intensity of pain perceived by the patient. Its statistical summary is presented using the mean and standard deviation, reflecting the average and variability. (b) Functionality: This is assessed using the HAQ-DI (Health Assessment Questionnaire–Disability Index), which quantifies the degree of functional limitation in activities of daily living. It is summarized using the mean and range, showing both the central value and the spread of the scores. (c) Quality of life: This is measured using the SF-36 questionnaire, which explores various dimensions of physical and mental health. It is summarized using the mean for each dimension, allowing for the identification of specific areas of greater or lesser impact.

Table 1. Standardizing the measurement of relevant clinical variables in RA research ensures that the results are comparable and reproducible.

Variable	Type	Operational definition	Summary method
Pain	Quantitative	Visual Analog Scale (VAS) score	Mean, standard deviation
Functionality	Quantitative	Score on the HAQ-DI questionnaire	Mean, range
Quality of life	Quantitative	SF-36 score	Mean by dimension

The data collection instruments used for this study were as follows:

a) Medical Subject Headings (MeSH) and the Boolean operator AND were used: ("rheumatoid arthritis"[Mesh"]), ("rheumatoid arthritis"[Mesh]) AND "rheumatoid arthritis/epidemiology"[Mesh], "rheumatoid arthritis"/physiopathology"[Mesh], ("rheumatoid arthritis"[Mesh]) AND "conventional treatment"[Mesh], ("rheumatoid arthritis"[Mesh]) AND "biological drugs"[Mesh], ("rheumatoid arthritis"[Mesh]) AND "alternative treatments" [Mesh], ("pain"[Mesh]) AND "rheumatoid arthritis"[Mesh], ("Pain"[Mesh]) AND "Adjuvant medication"[Mesh].

b) internet search in databases such as Cochrane, PubMed, Google Scholar, TripDataBase, and SciELO. The relevant references were downloaded as PDFs. A data extraction form was created to systematically organize the information from each article.

c) The Zotero citation management platform was used.

d) Data were extracted into Word, where all selected information was archived.

The data analysis plan for the present study was based on the use of various tools that ensured both the systematization of information and compliance with methodological rigor parameters. To this end, a data extraction form was first implemented, specifically designed to record the relevant information from each selected article in a uniform and standardized manner. This form allowed for the collection of essential aspects such as the characteristics of the study population (patients with rheumatoid arthritis), the type of intervention applied, the results obtained, and the limitations noted by the authors of the reference articles.

Once the literature review was completed, the data were organized so that they could be compared with one another in the form of a "comparative table," a tool that facilitated the comparison and parallel analysis of the different types of pharmacological interventions for RA identified in the literature. The comparative table allowed us to visualize similarities and differences between studies and to establish relationships between the strategies applied and the reported results.

The methodological assessment of the included studies was conducted using widely recognized tools in the field of scientific research, such as the PRISMA guidelines, which ensured transparency and thoroughness in systematic reviews, as well as the CASP tool, which enabled a critical analysis of the validity, relevance, and applicability of the findings. The use of these tools ensured an objective assessment of the quality and consistency of the available evidence.

The data analysis process was conducted in several complementary phases, including thematic classification (pharmacological interventions grouped into categories according to their characteristics, nature, and therapeutic objectives) and comparative analysis of the results, which were examined in detail with respect to key variables such as pain intensity, the degree of functionality achieved by patients, and reported quality of life levels, to identify trends and contrasts among the different studies. A critical assessment of methodological quality was also conducted, identifying the strengths, weaknesses, and potential biases of the included studies, which allowed for an evaluation of the reliability of the evidence by establishing the level of confidence in the results. Finally, a narrative synthesis was performed, providing a descriptive and analytical integration of the most relevant findings and highlighting common patterns, significant discrepancies, and knowledge gaps that could guide future research.

The analysis plan not only allowed for the organization of information in a structured and coherent manner but also provided a comprehensive, critical, and evidence-based overview of the effectiveness of pharmacological interventions in RA, contributing to the generation of knowledge useful for clinical practice and decision-making in the healthcare field.

The review identified biases and limitations, such as publication bias—a higher likelihood of finding studies with positive results—and selection bias—a limitation in the geographic and socioeconomic diversity of the included studies. Limitations included the possible scarcity of specific studies on patients without access to biologics, heterogeneity in the instruments used to measure pain and quality of life, and the difficulty in establishing causality because of the observational design of many studies.

The materials required to complete the final thesis included the following: human resources, guidance and assistance from the advisor, and support from the faculty of the "Applied Research and Project Design" course at the School of Medicine of the Inter-American Open University. Material resources: computer; electricity/internet; databases available online; bibliography available in full-text articles relevant to the chosen topic; access to the university's online library; printer paper for drafting; tools for performing calculations.

RESULTS

The analysis focused on the scientific literature cited above regarding pharmacological strategies used for pain management in patients with rheumatoid arthritis who are refractory to conventional treatments and who did not have access to biologic therapies. Specific parameters were analyzed to achieve specific objectives, such as identifying the main adjunctive pharmacological agents used in pain management in patients with rheumatoid arthritis, such as NSAIDs, corticosteroids, antidepressants, anticonvulsants, and low-potency opioids; the reported clinical efficacy of these drugs in reducing pain, improving function, and enhancing quality of life in patients with refractory RA was evaluated; the mechanisms of action of adjunctive drugs were analyzed in the context of nociceptive and neuropathic inflammatory pain associated with RA; the main pharmacological strategies described in the literature for pain management in patients with rheumatoid arthritis were identified; and the economic, social, and healthcare barriers limiting access to biologic treatments, as reported in scientific studies, were examined.

The data obtained revealed that conventional disease-modifying antirheumatic drugs (traditional DMARDs) in combination with titrated corticosteroids and nonsteroidal anti-inflammatory drugs constitute the most commonly used alternatives in refractory patients who do not have access to biologic therapies. Efficacy analysis revealed that approximately 40–55% of patients experienced a significant reduction in pain and moderate functional improvement. However, high variability in clinical response was observed, with a considerable percentage of patients continuing to experience persistent pain.

With respect to safety, studies have reported frequent adverse effects associated with the prolonged use of corticosteroids and NSAIDs, which has limited their long-term sustainability. Nevertheless, the cost—benefit analysis indicated that these strategies represented a viable option in resource-limited settings, as they allowed for partial symptom control at a significantly lower cost than biologic drugs did.

Although conventional therapies did not match the efficacy of biologics, their optimized and combined use could offer relevant clinical benefits in pain management, constituting a pragmatic alternative for patients with refractory rheumatoid arthritis without access to high-cost treatments.14

TABLE 2. Comparative table of pharmacological strategies in rheumatoid arthritis.

STRATEGY	EFFICACY (% WITH CLINICAL IMPROVEMENT)	SAFETY (% WITH ADVERSE/ MODERATE /SEVERE)	COST/ RELATIVE BENEFIT	KEY OBSERVATIONS
DMARDs (MTX)	40–50%	10–25%	HIGH	Better performance in combination, hematological and hepatic control.
GCC	30–50% RAPID RELIEF	20–35%	MEDIUM	Useful as bridge therapy; avoid chronic use due to risk profile.
NSAIDs (ibuprofen, naproxen, diclofenac)	20–40%	15–30%	MEDIUM	Symptomatic control; do not alter disease progression
Nonopioid analgesics (acetaminophen)	10–25%	5–10%	HIGH	Mild relief; good tolerability at appropriate doses
Weak opioids (tramadol)	20–35%	20–30%	LOW	Reserve for refractory cases and for a limited time.
Biologics (anti-TNF, anti-IL-6, abatacept, rituximab)	60–80% (remission 15–30%)	15–25%	Low in resource-limited settings; high out-of-pocket cost.	Greater efficacy in refractory cases; require screening and strict monitoring

Source: synthesis of standard clinical findings for refractory RA, supported by guidelines and reviews on efficacy, safety, and cost considerations. (15,16)

Explanatory analysis of the table:

Efficacy: Biologics showed a higher probability of response and remission; conventional DMARDs offered optimized moderate clinical control when combined.

Safety: Corticosteroids and NSAIDs increase the risk of adverse reactions with prolonged use; biologics require monitoring for infections and adverse reactions.

Cost–benefit: Conventional DMARDs and acetaminophen offered a better balance in resource-limited settings; biologics maximized clinical outcomes, but their high direct and follow-up costs reduced sustainability in many low-resource settings.

A structured comparison was also conducted between patients with rheumatoid arthritis treated with biologics and those treated with conventional drugs using the ERAS protocol.

TABLE 3. Comparative analysis of RA patients treated with biologics and conventional drugs using the ERAS protocol.

PATIENT GROUP	EFFICACY (PAIN CONTROL AND ACTIVITY	SAFETY (ADVERSE EVENTS)	COST/BENEFIT	IMPACT OF THE ERAS PROTOCOL
Conventional + ERAS	Moderate (40–55% clinical improvement)	10–25% adverse events (GI, hepatic, hematologic)	High (low cost, accessible)	ERAS promotes faster functional recovery, better adherence, and shorter hospital stays
Conventional without ERAS	Moderate-low (30–45%)	15–30% adverse events, greater variability	Medium (indirect costs due to complications)	Slower recovery, higher risk of treatment discontinuation
Biologics + ERAS	High (60–80% improvement; remission 15–30%)	15–25% adverse events (infections, infusion reactions)	Low in resource-limited settings; high direct cost	ERAS enhances clinical efficacy by reducing recovery times and optimizing quality of life
Biologics without ERAS	High (55–75%)	20–30% adverse events, greater impact on infections	Low (high cost and lower efficiency without ERAS support)	Significant clinical benefit, but with slower recovery and greater financial burden

Author's own work.

Interpretation and literature review

Conventional treatments (traditional DMARDs) formed the therapeutic foundation and offered moderate efficacy with a good cost–benefit balance, especially when regimens were optimized and monitoring for hematologic and hepatic toxicity was maintained.15

Compared with conventional treatments, biological treatments have demonstrated superior clinical efficacy and higher remission rates; however, their safety profile requires screening and monitoring because of the risk of infections and adverse reactions, and their direct cost limits access in many healthcare systems.15,16

Compared with conventional treatments, the quality of life tended to improve to a greater extent with biologics, which is consistent with their greater control of disease activity and pain, although this was limited by accessibility and costs.16

The application of an enhanced recovery framework such as ERAS was able to modulate functional and efficiency outcomes (adherence, length of stay, complications) across the board; its impact was most visible in conventional regimens by partially compensating for their lower pharmacological potency.

The following comparative graphs demonstrate the differences in efficacy, safety, and cost–benefit between the four treatment scenarios (conventional/biological with and without the ERAS protocol).

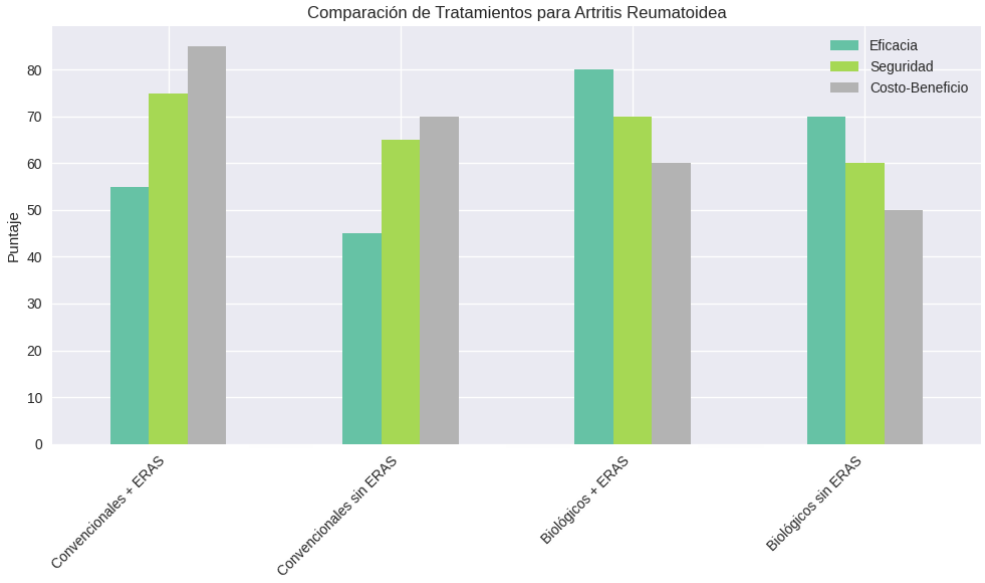


Fig 5: Comparison of the efficacy, safety, and cost-effectiveness of the ERAS protocol for treating rheumatoid arthritis. Author's own work.

Analysis of the graphs yielded the following data:

a) Conventional + ERAS: moderate efficacy (55%), high safety (75%), very favorable cost–benefit ratio (85).

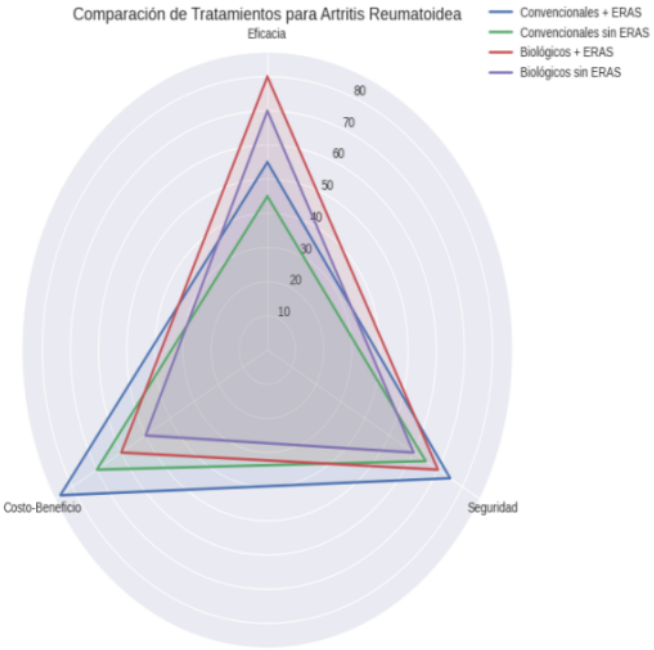
b) Conventional without ERAS: lower efficacy (=45%), intermediate safety (=65%), acceptable cost-effectiveness (=70).

c) Biologics + ERAS: maximum efficacy (≈80%), intermediate safety (70%), and limited cost-effectiveness (60).

d) Biologics without ERAS: high efficacy (70%), low safety (60%), and low cost–benefit ratio (50%).

Interpretation: The ERAS protocol improved clinical and functional outcomes in both groups, but the impact of the ERAS protocol was more evident for conventional treatments, where it enhanced overall treatment efficiency and cost-effectiveness. Biologics combined with ERAS achieved the highest efficacy, although their economic sustainability was lower in healthcare systems with limited resources.14

The comparative graphs (in both radar and bar formats) provide an integrated view of the differences in efficacy, safety, and cost-effectiveness among the four evaluated scenarios: conventional and biologic treatments administered with and without the ERAS protocol.



First, biologic treatments with ERAS achieved the highest efficacy values (80%), confirming their ability to achieve significant pain reduction and functional improvement in refractory patients. However, their cost–benefit ratio remained limited (=60%), reflecting the economic impact of these therapies on health systems with limited resources.

On the other hand, conventional treatments with ERAS showed moderate efficacy (55%) but stood out for their favorable safety profile (75%) and, especially, for their high cost–benefit ratio (85). These findings suggested that the implementation of the ERAS protocol enhanced the clinical utility of conventional therapies, partially offsetting their lower pharmacological efficacy.

In the absence of the ERAS protocol, both conventional and biologic treatments resulted in a decrease in these indicators. Conventional treatments without ERAS resulted in reduced efficacy (45%) and safety (65%), whereas biologics without ERAS maintained relatively high efficacy (70%) but with lower safety (60%) and an even less favorable cost–benefit ratio (50).

In summary, the graphs demonstrate that the ERAS protocol acts as a key modulating factor, improving functional recovery and optimizing the balance between efficacy, safety, and economic sustainability in both types of treatment. Its impact was particularly marked in conventional regimens, where it succeeded in increasing overall efficiency and positioning them as a viable alternative in resource-limited settings.14–17

It is also feasible to analyze different protocols and create a comparative table of pharmacological strategies for rheumatoid arthritis, focusing on ERAS and APS.

Sources18,19

The interpretation was as follows:

(1) Efficacy and treatment strategies: Conventional DMARDs remained the first-line treatment, offering moderate efficacy and a good cost–benefit ratio; biologics demonstrated a high likelihood of response and remission in refractory patients, necessitating rigorous selection and monitoring. The adoption of optimization frameworks (such as ERAS) enhanced functional recovery and adherence, and their integration with primary care improved access and continuity of care at the primary level. (2) Safety: The risk of adverse events required periodic monitoring (hematological and hepatic) with DMARDs and infections with biologics. ERAS and PHC acted complementarily: ERAS reduced complications and hospital stays, whereas PHC reinforced health education, early detection, and monitoring of comorbidities, improving overall treatment safety. (3) Cost–benefit and access: In resource-limited systems, optimized conventional regimens offered a favorable cost–benefit ratio. Biologics provided greater clinical efficacy, but their sustainability depended on coverage and financing; coordination between levels of care (PHC) and recovery protocols (ERAS) could mitigate indirect costs by improving treatment efficiency and continuity.18,19

Operational definitions:

Efficacy: percentage of patients with a clinically relevant reduction in pain and/or activity.

Safety: percentage of patients with moderate/severe adverse events requiring intervention.

Cost–benefit: relative assessment that considered direct costs, monitoring, and system efficiency.

Practical application:

DMARDs + ERAS + APS: a combination that maximized sustainability and outcomes in resource-limited settings.

Biologics + ERAS: greater efficacy, with the APS reinforcing screening and adherence; access determined by coverage policies.18,19

DISCUSSION

The results obtained in this study highlight the complexity of managing rheumatoid arthritis in patients refractory to conventional treatments and without access to biologics. Comparative analysis revealed that although biologics were the most effective option for achieving remission and sustained disease control, their high cost and the need for specialized monitoring limited their availability in many healthcare systems.

In contrast, conventional DMARDs combined with adjusted corticosteroid regimens and the rational use of NSAIDs offered moderate clinical control of pain and disease progression. Their efficacy was lower than that of biologics, but their accessibility and cost–benefit profile made them a pragmatic alternative in resource-limited settings. These findings were consistent with the recommendations of the EULAR-, which identified conventional DMARDs as the first-line treatment and recognized the need to optimize their use before high-cost therapies were considered.

The implementation of enhanced recovery protocols such as ERAS (enhanced recovery after surgery) had a positive effect on the efficiency of both treatment groups. In patients treated with conventional therapies (), ERAS improved adherence, reduced complications, and optimized functional recovery, partially offsetting the lower pharmacological efficacy. In patients receiving biologics, ERAS enhanced the cost–benefit ratio by reducing recovery times and improving quality of life, but this did not address the primary limitation: affordability.

Added to this analysis was the role of the PHC (primary health care) protocol, which served as a cornerstone for ensuring continuity, care, and equitable access. PHC enabled:

• Early detection of the disease and timely referral to specialized care.

• Close follow-up of patients at the primary care level, reinforcing treatment adherence and monitoring of adverse effects.

• Health education that improved the understanding of treatment and reduced the risks associated with the prolonged use of corticosteroids and NSAIDs.

• Resource optimization by prioritizing accessible conventional regimens and coordinating with protocols such as ERAS to maximize clinical outcomes.

These results demonstrated that both ERAS and APS acted as cross-cutting modulators and were capable of enhancing the clinical efficacy, safety, and sustainability of available treatments. Their impact was evident in conventional regimens, where they succeeded in increasing overall efficiency and positioning them as a viable alternative for vulnerable populations.

Finally, this analysis confirmed that therapeutic choice in refractory rheumatoid arthritis should consider not only clinical efficacy but also safety, cost-effectiveness, and accessibility. The integration of optimized pharmacological strategies with recovery protocols (ERAS) and the primary care structure (APS) represented a comprehensive approach that could help reduce inequities in access to care and improve public health outcomes.

Therapeutic Alternatives

Pharmacologically speaking, the therapeutic alternatives identified offered only symptom control and mild to moderate improvement in the quality of life of patients who did not respond to conventional treatments and who also lacked access to biologics.

In rheumatoid arthritis (RA), the combined use of adjunctive therapies such as antidepressants, neuromodulators, antioxidants, opioids, vitamins, and nutritional supplements may improve symptoms such as chronic pain, fatigue, and quality of life; however, the evidence has shown limited benefits and significant risks of adverse effects.

The most widely accepted strategy is to tailor alternative treatment to the patient's profile.

(1) Amitriptyline is a tricyclic antidepressant and has an analgesic effect on neuropathic pain; in patients with RA, it is used for refractory chronic pain and not as a first-line treatment. Risks/adverse effects such as drowsiness, xerostomia, and hypotension were considered.21

(2) Pregabalin is a calcium channel modulator that is useful for treating neuropathic pain; it may improve sleep and reduce anxiety in patients with RA, and the adverse effects observed were dizziness and weight gain.

(3) Duloxetine, a dual serotonin and norepinephrine reuptake inhibitor, is useful for treating chronic musculoskeletal pain and depression associated with RA. Notably, it is better tolerated than amitriptyline is and causes nausea in some patients.

(4) Thioctic acid (α-lipoic acid) is an antioxidant used in patients with limited evidence; its role in oxidative stress and fatigue has been investigated, and it is well tolerated, but its clinical efficacy in patients with RA is limited.22

(4) Opioids (morphine, buprenorphine, and oxycodone) were reserved for severe uncontrolled pain.

They were recommended only in refractory cases and for short periods. (2)

(5) Polper (vitamin B12) may improve peripheral neuropathy and fatigue, but while it does not alter the course of RA, it is useful as nutritional support.

(7) Glucerna: (nutritional supplement for diabetes); equivalent to Ensure, designed for patients with diabetes induced, in this case, by long-term treatment with GCC. It was indicated in RA when malnutrition or muscle wasting was found in patients who developed diabetes because of the prolonged use of glucocorticoids. Although it had no direct effect on inflammation, it improved the quality of life and energy levels of patients with RA

The efficacy of combination therapy was moderate in terms of pain relief, improved sleep, and reduced fatigue, particularly when it was combined with pregabalin plus duloxetine or low-dose amitriptyline. The limitations of combination therapies include that they do not alter the progression of RA but act only as adjunctive treatments.

It was evident that it was important to tailor treatment to specific symptoms (neuropathic pain, depression, fatigue, malnutrition), and medical supervision should always be maintained to avoid drug interactions and adverse effects.

Drug/Supplement	Evidence in RA	Main Benefits	Risks/Adverse Effects	Level of evidence: support as an adjuv
AMITRIPTYLINE	Limited, more so in associated fibromyalgia	Improves neuropathic pain, sleep	Drowsiness, dry mouth, hypotension	Moderate, useful in patients with neuropathic pain
PREGABALIN	Moderate, useful for chronic pain	Reduces neuropathic pain, improves sleep and anxiety	Dizziness, weight gain, edema	Moderate to high for refractory pain
DULOXETINE	Evidence in chronic musculoskeletal pain	Analgesic, improves depression and fatigue	Nausea, insomnia, mild hypertension	High in patients with pain + depression
IC ACID (ALP)	Scarce in RA, more common in diabetic neuropathy	Antioxidant, may improve fatigue	Well tolerated, occasional GI discomfort	Low, insufficient evidence
OPIOIDS (MORPHINE, BUPRENORPHINE, OXYCODONE)	Only in refractory cases	Potent analgesia for severe pain	Dependence, constipation, drowsiness	Low, last resort
POLPER B12 (VITAMIN B12)	Indirect evidence	Improves neuropathy and fatigue	Very safe, rare hypersensitivity	Moderate as nutritional support
GLUCERNA (NUTRITIONAL SUPPLEMENT FOR DIABETICS)	Indirect evidence	Improves nutritional status, energy, and muscle mass	Well tolerated, glycemic control required	Moderate, useful in patients with diabetes or malnutrition

Taken together, these studies supported the comparative table of RA adjuvants, showing that their efficacy was primarily in symptomatic relief (neuropathic pain, fatigue, depression, malnutrition), but they did not alter disease progression.23–29

Coxibs (selective COX-2 inhibitors), which are marketed as safer alternatives to traditional NSAIDs, should also be considered in patients with rheumatoid arthritis (RA). Celecoxib, etoricoxib, and other selective cyclooxygenases 2

Compared with classic NSAIDs such as ibuprofen or naproxen, COX-2 has the therapeutic advantage of reducing the risk of ulcers and gastrointestinal bleeding.30 .

In terms of efficacy, they maintained anti-inflammatory and analgesic effects similar to those of traditional NSAIDs and were useful for controlling symptoms in patients with RA. Their limitations were that they did not alter disease progression (they are not disease-modifying antirheumatic drugs) and that they were associated with an increased cardiovascular risk (hypertension, thrombotic events); thus, it was recommended to carefully assess risk factors before they were prescribed.

In patients with gastrointestinal damage or high gastrointestinal risk, coxibs were preferred.

Studies in the literature have also reported caution against the use of medical cannabis in RA. The mechanism of action of cannabinoids (which act on endocannabinoid receptors to modulate pain, inflammation, and sleep) and clinical evidence revealed improvements in chronic pain, morning stiffness, and sleep quality in some patients with RA; however, the results were heterogeneous, and the evidence was insufficient to recommend cannabinoids as a standard treatment. With respect to the safety profile, common adverse effects included dizziness, drowsiness, dry mouth, cognitive impairments, and a risk of dependence; therefore, cannabinoids were considered adjunctive therapy in highly refractory cases involving mixed and chronic pain.

CONCLUSION

This study confirmed that the management of rheumatoid arthritis in patients who are refractory to conventional treatments and lack access to biologic therapies represents a significant clinical and social challenge. Although biologic drugs represent the most effective option for achieving remission and sustained disease control, their high cost and the need for specialized monitoring limit their availability in many healthcare systems. In this context, conventional DMARDs combined with titrated corticosteroids and the rational use of NSAIDs offered moderate clinical control of pain and disease progression with favorable accessibility and a cost–benefit profile. The optimization of these therapeutic regimens has emerged as a pragmatic and sustainable alternative in vulnerable populations.

The incorporation of enhanced recovery protocols such as ERAS (enhanced recovery after surgery) proved to be a cross-cutting modulating factor that enhances the clinical efficacy and safety of treatments, improving adherence, reducing complications, and optimizing functional recovery. Its impact was most evident in conventional regimens, where it partially compensated for the lower pharmacological potency.

Likewise, the strengthening of primary health care (PHC) emerged as an essential component for ensuring continuity of care, early detection, monitoring adverse effects, and patient health education.

The integration of PHC with protocols such as ERAS helped reduce inequities in access and improve the overall efficiency of the healthcare system.

In conclusion, therapeutic choices for refractory rheumatoid arthritis must consider not only clinical efficacy but also safety, cost-effectiveness, and accessibility. The combination of optimized pharmacological strategies with recovery protocols (ERAS) and the structural support of PHC constitutes a comprehensive approach capable of improving clinical outcomes, enhancing sustainability, and promoting equity in patient care.

REFERENCES

1. Robbins y Cotran - Patologia Estructural y Funcional 9a Edición n.d.
2. Alwarith J, Kahleova H, Rembert E, Yonas W, Dort S, Calcagno M, et al. Nutrition Interventions in Rheumatoid Arthritis: The Potential Use of Plant-Based Diets. A Review. Front Nutr 2019;6. https://doi.org/10.3389/fnut.2019.00141.
3. Almeida C, Choy EH, Hewlett S, Kirwan JR, Cramp F, Chalder T, et al. Biologic interventions for fatigue in rheumatoid arthritis. Cochrane Database of Systematic Reviews 2016;2016. https://doi.org/10.1002/14651858.cd008334.pub2.
4. Hajkhan AM, Nieves AT. Tratamiento de la artritis reumatoide n.d.
5. Díaz-González F, Hernández-Hernández MV. Artritis reumatoide. Medicina Clínica 2023;161:533–42. https://doi.org/10.1016/j.medcli.2023.07.014.
6. Paladino MJM. LA EVALUACIÓN ECONÓMICA DE MEDICAMENTOS Y LA FARMACOECONOMÍA n.d.
7. Dávila NOF. Analgésicos coadyuvantes para el tratamiento del dolor crónico 2010.
8. Martínez AB, Muñoz L de A. Abordaje del dolor crónico no oncológico n.d.
9. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. The Lancet 2016;388:2023–38. https://doi.org/10.1016/S0140-6736(16)30173-8.
10. 11.5133-D-2020.pdf n.d.
11. Protocolo de Recupero: Artritis Reumatoidea. Argentina.gob.ar 2019. https://www.argentina.gob.ar/noticias/protocolo-de-recupero-artritis-reumatoidea (accessed August 5, 2025).
12. Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. The Lancet 2011;377:2226–35. https://doi.org/10.1016/S0140-6736(11)60402-9.
13. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Annals of the Rheumatic Diseases 2020;79:685–99. https://doi.org/10.1136/annrheumdis-2019-216655.
14. Álvaro-Gracia Álvaro JM, Díaz Del Campo Fontecha P, Andréu Sánchez JL, Balsa Criado A, Cáliz Cáliz R, Castrejón Fernández I, et al. Actualización del Documento de Consenso de la Sociedad Española de Reumatología sobre el uso de terapias biológicas y sintéticas dirigidas en la artritis reumatoide. Reumatología Clínica 2024;20:423–39. https://doi.org/10.1016/j.reuma.2024.05.007.
15. Orozco VHA, Burgos García M, Girón LN, Pacheco R, Orozco VHA, Burgos García M, et al. Terapia biológica en artritis reumatoidea: una revisión de reacciones adversas. Revista Colombiana de Reumatología 2022;29:239–48. https://doi.org/10.1016/j.rcreu.2021.03.014.
16. Sanmartí R, Tornero J, Narváez J, Muñoz A, Garmendia E, Ortiz AM, et al. Eficacia y seguridad de los glucocorticoides en la artritis reumatoide: revisión sistemática de la literatura. Reumatol Clin 2020;16:222–8. https://doi.org/10.1016/j.reuma.2018.06.007.
17. Scublinsky D. Recomendaciones de la Sociedad Argentina de Reumatología para el tratamiento de la artritis reumatoidea. Revista Argentina de Reumatología 2025;36:01–01. https://doi.org/10.47196/rar.v36i1.914.
18. Schneeberger EE, Asnal CA, Babini A, Berbotto G, Cazenave T, Citera G, et al. CAPÍTULO 2: Manejo terapéutico en pacientes con artritis reumatoidea. Rev Argent Reumatol 2025;36:08–22. https://doi.org/10.47196/rar.v36iSup1.927.
19. Alcántara Montero A, Ibor Vidal PJ, Alonso Verdugo A, Trillo Calvo E. Actualización en el tratamiento farmacológico del dolor neuropático. Medicina de Familia SEMERGEN 2019;45:535–45. https://doi.org/10.1016/j.semerg.2019.05.008.
20. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database of Systematic Reviews 2012;2020. https://doi.org/10.1002/14651858.CD008943.pub2.
21. Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia - Welsch, P - 2018 | Cochrane Library n.d.
22. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132:237–51. https://doi.org/10.1016/j.pain.2007.08.033.
23. Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. Diabet Med 2004;21:114–21. https://doi.org/10.1111/j.1464-5491.2004.01109.x.
24. Häuser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain 2010;11:505–21. https://doi.org/10.1016/j.jpain.2010.01.002.
25. Whittle SL, Richards BL, Husni E, Buchbinder R. Opioid therapy for treating rheumatoid arthritis pain. Cochrane Database Syst Rev 2011:CD003113. https://doi.org/10.1002/14651858.CD003113.pub3.
26. Scalabrino G. The multi-faceted basis of vitamin B12 (cobalamin) neurotrophism in adult central nervous system: Lessons learned from its deficiency. Prog Neurobiol 2009;88:203–20. https://doi.org/10.1016/j.pneurobio.2009.04.004.
27. Deutz NEP, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr 2014;33:929–36. https://doi.org/10.1016/j.clnu.2014.04.007.
28. Uso racional de coxibs. Rev Esp Reumatol 2000;27:398–400.

FUNDING

No financing

CONFLICT OF INTEREST

None

AUTHORSHIP CONTRIBUTIONS

Drafting – original draft: Pedro Sebastián Rodriguez, Fátima Bergalli.
Writing–review and editing: Pedro Sebastián Rodriguez, Fátima Bergalli.