Evaluation of biologic treatment in rheumatoid arthritis in Peruvian older adults: A systematic review

Evaluación del tratamiento biológico en la artritis reumatoide en adultos mayores peruanos: una revisión sistemática

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease that mainly affects older adults, significantly impacting their functionality and quality of life. Although biological treatments have demonstrated efficacy in controlling the disease, their access in Peru continues to be limited due to economic, structural, and infrastructural barriers. Therefore, the objective of this study was to evaluate the efficacy, safety, and accessibility of biological treatments in Peruvian older adults with RA, identifying the main challenges and opportunities to optimize their implementation in the Peruvian health system. A systematic review of 269 studies published between 2015 and 2024 in databases such as PubMed, Scopus, SciELO and LILACS was carried out, from which 7 articles were selected that addressed the use of these treatments, their adverse effects and access in the Peruvian context. The results reveal that, although biological treatments are effective in controlling RA in older adults, challenges persist in terms of safety, adherence, and access. Barriers such as high cost, limited availability in less complex hospitals, and difficulties associated with access protocols were identified. The adoption of biosimilars, the decentralization of care, and the strengthening of telemedicine are emerging as key strategies to expand coverage and optimize the management of the disease in this vulnerable population.

Keywords: rheumatoid arthritis, biologic treatment, older adults.

Resumen

La artritis reumatoide (AR) es una enfermedad inflamatoria crónica que afecta principalmente a los adultos mayores, impactando significativamente su funcionalidad y calidad de vida. Si bien los tratamientos biológicos han demostrado eficacia en el control de la enfermedad, su acceso en el Perú continúa siendo limitado debido a barreras económicas, estructurales y de infraestructura. Por ello, el presente estudio tuvo como objetivo evaluar la eficacia, seguridad y accesibilidad de los tratamientos biológicos en adultos mayores peruanos con AR, identificando los principales retos y oportunidades para optimizar su implementación en el sistema de salud peruano. Se realizó una revisión sistemática de 269 estudios publicados entre 2015 y 2024 en bases de datos como PubMed, Scopus, SciELO y LILACS, de los cuales se seleccionaron 7 artículos que abordaban el uso de estos tratamientos, sus efectos adversos y el acceso en el contexto peruano. Los resultados revelan que, aunque los tratamientos biológicos son efectivos en el control de la AR en adultos mayores, persisten desafíos en cuanto a seguridad, adherencia y acceso. Se identificaron barreras como el alto costo, la disponibilidad limitada en hospitales de menor complejidad y las dificultades asociadas a los protocolos de acceso. La adopción de biosimilares, la descentralización de la atención y el fortalecimiento de la telemedicina se perfilan como estrategias clave para ampliar la cobertura y optimizar el manejo de la enfermedad en esta población vulnerable.

Palabras clave: artritis reumatoide, tratamiento biológico, adultos mayores.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that primarily affects middle-aged individuals, although its prevalence has increased among older adults due to rising life expectancy (Nooh et al., 2024). The treatment of RA that begins in older age presents particular challenges due to the specific characteristics of the disease in this age group, such as the presence of comorbidities, the concurrent use of multiple medications (polypharmacy), and the physiological changes associated with aging (Dalal et al., 2019).

Recent research has shown that advanced age can modify the response to biological treatments. Older adults often present with higher disease activity at the initiation of treatment, as well as a greater use of steroids, factors that may negatively impact the efficacy and safety of these therapies. In particular, tumor necrosis factor (TNF) inhibitors have demonstrated less favorable efficacy results in older adults compared to younger patients. This difference may be explained by the presence of additional comorbidities, such as hypertension, diabetes, or osteoporosis, which alter therapeutic responses (Freitas et al., 2020; Ishchenko & Lories, 2016).

Biological agents, although less frequently used in older patients, have proven effective in the treatment of RA. However, older patients tend to have higher disease activity at the start of treatment and a greater use of steroids, which can influence the efficacy and safety of these treatments (Dalal et al., 2019; Freitas et al., 2020). Specifically, TNF inhibitors have shown less favorable efficacy results in older patients compared to their younger counterparts (Ishchenko & Lories, 2016).

RA is one of the leading causes of disability in older adults, affecting approximately 0.5% to 1% of the global population (Miguel-Lavariega et al., 2023). In Peru, its impact on the elderly is significant due to the lack of early diagnosis and limitations in access to treatment. Biological drugs have improved the prognosis of RA, but their use in older adults poses challenges related to safety, adherence, and access (Alarcón, 2022).

Regarding the access and use of disease-modifying biological drugs (DMARDs) in older adults with RA, several obstacles have been identified. For instance, an observational study on patients with RA, ankylosing spondylitis, and psoriatic arthritis found that treatment administration by a family member or caregiver was associated with lower adherence to the therapeutic regimen (Núñez-Rodríguez et al., 2021).

Although tolerance to biotherapies in older patients is generally adequate, this group presents a higher risk of developing serious adverse effects, such as infections, compared to younger patients (Dalal et al., 2019; Freitas et al., 2020; Sahimi et al., 2022). Some studies indicate that older adults are more likely to experience adverse events that may lead to treatment discontinuation (Murota et al., 2016; Vela et al., 2020).

In this context, the objective of this review was to evaluate the efficacy, safety, and access to biological treatments in Peruvian older adults with RA, identifying the main challenges and opportunities to optimize their implementation within the Peruvian healthcare system.

Methodology

A systematic search of scientific literature was conducted in recognized academic databases, such as PubMed, Scopus, SciELO, and LILACS. Specific search terms in English were employed, such as “biologic therapy AND rheumatoid arthritis AND elderly AND Peru.” The search was limited to articles published between

2015 and 2024 that evaluated aspects related to the efficacy, safety, and access to biological treatments in older adults with rheumatoid arthritis in the Peruvian context.

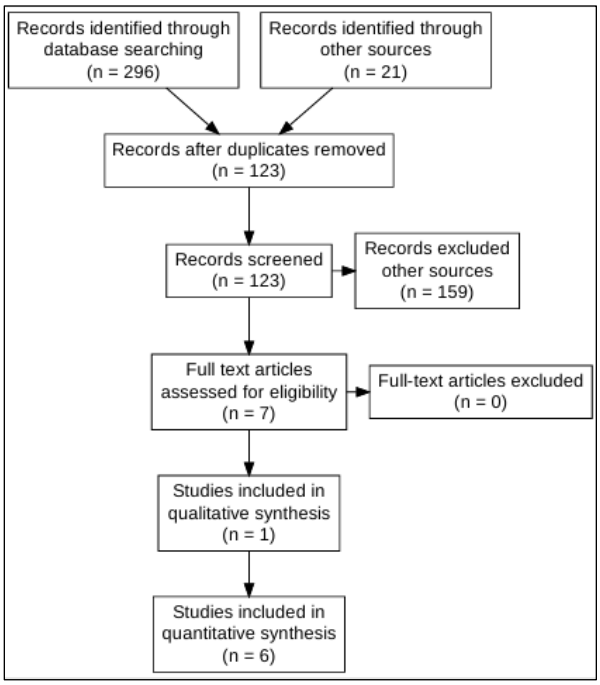
Inclusion criteria. The studies included in this review met the following criteria: a) original studies addressing the use of biological treatments in patients with rheumatoid arthritis; b) research conducted on older adults (≥ 65 years) diagnosed with RA; c) articles published between 2015 and 2024; and d) studies providing information related to efficacy, safety, adverse effects, or access to biological treatments in the Peruvian context.

Exclusion criteria. Studies were excluded if they did not meet the following aspects: a) research focused on pediatric or younger populations; b) articles that did not specifically address biological treatments for rheumatoid arthritis; c) studies that did not provide relevant data on the Peruvian older adult population or did not cover aspects of safety or access; and d) publications that were not peer-reviewed or did not meet minimum standards of methodological quality.

The initial search identified a total of 269 articles. After applying the inclusion and exclusion criteria, 37 articles were selected for full-text review. Of these, 25 studies were excluded for reasons such as low thematic relevance, result duplication, or lack of specific information for the Peruvian context. Ultimately, 7 studies that met all established criteria were included for analysis and discussion. The selected studies consisted of clinical trials, observational studies, and systematic reviews pertinent to the investigated topic.

To ensure the quality and reliability of the studies included in this review, a critical evaluation of each was conducted using the Jadad Scale (for clinical trials) and the STROBE Checklist (for observational studies). This procedure ensured the selection of studies with adequate methodological quality, thus strengthening the validity of the results obtained in this review.

Figure 1 *PRISMA Flow Diagram*



During the review process, several relevant limitations were identified. Firstly, many of the included studies did not report their methodology in detail, which hindered a rigorous critical evaluation of their methodological quality. Despite the application of tools such as the Jadad Scale for clinical trials and the STROBE checklist for observational studies, it was not possible in some cases to fully assess the risk of bias, which could affect the internal validity of certain findings.

Moreover, while general comorbidities commonly present in the older adult population with rheumatoid arthritis—such as hypertension, diabetes mellitus, and osteoporosis—were addressed, no studies specifically explored the individual impact of these comorbidities on the therapeutic response to biological treatments. This gap limits subgroup analysis and reduces the ability to draw differential conclusions for populations with particular

clinical conditions. These limitations should be considered when interpreting the results of this review and reinforce the need for future research with a more detailed methodological approach, including specific analyses by comorbidity and greater control of bias risk.

Results and discussion

Biological treatments, such as TNF-α inhibitors (adalimumab, infliximab, etanercept), IL-6 inhibitors (tocilizumab), and T-cell co-stimulation inhibitors (abatacept), have demonstrated efficacy in reducing inflammation and improving functionality in older adults with RA (Marenco de la Fuente & Solís Díaz, 2009; Tornero Molina et al., 2020). However, various studies suggest that the therapeutic response to biologics may be less robust in older adults due to immunosenescence and the accumulation of comorbidities such as hypertension, diabetes, and osteoporosis, which could interfere with treatment efficacy (Navas & Serna, 2023).

Older adults treated with biological therapies exhibit a higher risk of serious infections, such as reactivated tuberculosis and pneumonia, compared to younger adults. This risk is exacerbated by the frequent use of corticosteroids, which increases bone fragility and the likelihood of serious adverse events. The reviewed literature emphasizes the need for constant monitoring in this population, prioritizing an individualized assessment of the risk-benefit relationship before initiating these treatments (Calvet et al., 2021a; Freitas et al., 2020).

One of the most significant concerns regarding biological treatments in older adults is the increased risk of serious infections, such as tuberculosis, pneumonia, and urinary tract infections. TNF-α inhibitors (such as adalimumab, infliximab, and etanercept) and other biologics that suppress the immune system increase susceptibility to such infections. In older adults, immunosenescence reduces the body's ability to combat these infections, heightening the risk. While all biological treatments carry a risk of serious infections, TNF-α inhibitors appear to be the most closely associated with an increased incidence of serious infections in older adults compared to other biologics, such as IL-6 inhibitors (tocilizumab), which show a more favorable safety profile in some studies (Freitas et al., 2020; Dalal et al., 2019).

The use of biological therapies has also been associated with cardiovascular adverse effects, especially in older adults with pre-existing comorbidities. TNF-α inhibitors, while effective in reducing inflammation in rheumatoid arthritis, have also been linked to an increased cardiovascular risk in some studies (Núñez-Rodríguez et al., 2021). Older adults with RA using biological treatments may be more susceptible to cardiovascular adverse effects due to the presence of comorbidities such as hypertension and diabetes, which are more common in this population (Greenberg et al., 2011; Avina-Zubieta et al., 2012; Tong et al., 2023; Liao, 2016).

The prolonged use of corticosteroids, often administered alongside biological treatments, is closely linked to the risk of osteoporosis and fractures. Older adults already have an elevated risk of bone fragility, and the combined use of biologics and corticosteroids significantly increases this risk (Arriagada, 2004; Calvet et al., 2021b; Freitas et al., 2020; Liao, 2016).

TNF-α inhibitors and some anti-IL-6 biologics, such as tocilizumab, have been associated with hepatic adverse effects, including hepatotoxicity and reactivation of hepatitis B virus. These effects may be more pronounced in older adults due to age-related declines in liver function and potential interactions with other medications used to manage comorbidities such as hypertension and diabetes. Regular monitoring of liver function is essential in older patients receiving these biological treatments to detect and manage any alterations promptly (Studenic et al., 2023).

Skin reactions are common adverse effects associated with the use of biologics, particularly TNF-α inhibitors. These reactions may manifest as rashes or allergic reactions at the injection site. Although generally not severe, they can affect the quality of life of patients. Comparative studies have shown that anti-TNF biologics and IL-6 inhibitors (such as tocilizumab) have a higher incidence of skin-related effects. This increased susceptibility could be an additional concern in older adults, who often have more sensitive skin (Hernández et al., 2013; Sheppard et al., 2017).

Table 1 *Comparison of adverse effects by biological treatment*

Biological Treatment	Risk of Infections	Cardiovascular Risk	Osteoporosis/Fragility	Hepatic Effects	Skin Reactions
TNF-α Inhibitors (adalimumab,	High	High	High	Moderate	High

infliximab, etanercept)					
IL-6 Inhibitors (tocilizumab)	Moderate	Low	Low	Low	Moderate
Abatacept	Moderate	Low	Low	Low	Low

Biological treatments have proven effective in managing RA in older adults, but adverse effects can vary depending on the type of biologic used. TNF-α inhibitors tend to be more associated with risks of severe infections, cardiovascular issues, and bone fragility in older adults, while IL-6 inhibitors and abatacept show a more favorable safety profile in these areas.

Despite their therapeutic benefits, access to biological treatments for RA in older adults in Peru faces multiple barriers. The high cost of medications poses a significant limitation. Biological treatments can exceed $10,000 USD annually, restricting their availability in the public sector. A study in Peru estimated that the comprehensive cost of treatment over 2.5 years amounts to S/. 275,970,912 for all patients nationwide, approximately $68,013,276 per patient (Echevarría Zárate, 2008).

The availability of these treatments is limited to high-complexity hospitals, primarily located in Lima and a few regional capitals. A report from the Ministry of Health of Peru highlights the availability of essential medications in healthcare facilities. Although the distribution of biological treatments for RA is not specifically mentioned, it notes that medication availability varies by care level and region. This suggests that certain specialized medications may be more accessible in high-complexity hospitals in urban areas like Lima, limiting access in other parts of the country (Ministerio de Salud, 2021). Additionally, coverage under the Integral Health Insurance (SIS) and EsSalud, while including some biological treatments, is constrained by protocol restrictions and administrative bureaucracy, delaying or impeding timely access.

Geographical inequality is another critical barrier. In rural areas of Peru, access to rheumatologists and advanced therapies is virtually nonexistent, perpetuating disparities in medical care. This situation is exacerbated by the lack of public policies that promote equitable distribution of specialized services and high-cost medications, primarily affecting older adults with chronic diseases like RA.

A study on systemic lupus erythematosus in Peru highlights that “limited access to rheumatology specialists in rural areas of the country exacerbates this situation” (Nikolopoulos & Parodis, 2023). Furthermore, the distribution of advanced therapies is uneven. A report from the National Association of Medicine of Peru states that “access to the best options and therapeutic schemes must be expanded to the Peruvian population, especially for those with fewer resources” (Alarcón, 2022). These geographic disparities in rheumatological care reflect the need for health policies that promote equity in access to specialized services and advanced therapies throughout the country.

In light of this scenario, various strategies have been proposed to improve the situation. One of these is the incorporation of biosimilars, which offer a lower-cost therapeutic alternative without compromising efficacy or safety. The General Directorate of Medicines, Supplies, and Drugs (DIGEMID) of the Peruvian Ministry of Health defines biosimilar products as those that, in terms of quality, safety, and efficacy, are similar to a reference biological product. This regulation facilitates the introduction of biosimilars to the market, promoting competition and potentially reducing treatment costs (Ministerio de Salud, 2016; Ortiz-Prado et al., 2020; Elena Lozano, 2022).

Strengthening telemedicine is another strategy. Remote consultations with rheumatologists could facilitate monitoring and treatment optimization. The Delphi Consensus on the use of telemedicine in rheumatology highlights that telemedicine (TM) is beneficial for monitoring patients with RA who have low disease activity or are in remission. It also notes that TM can alleviate the burden of in-person care in rheumatology, allowing for more efficient and accessible care (Graña Gil et al., 2024g; Tornero-Molina et al., 2020).

Additionally, implementing education and adherence programs targeted at patients and caregivers is recommended, as the lack of information and support negatively affects therapeutic adherence (Riemsma et al., 2003; Pérez et al., 2020). This systematic review concludes that education directed at patients with RA has positive short-term effects on disability, joint count, global patient assessment, psychological status, and depression (Riemsma et al., 2003; Pérez et al., 2020; Juan Mas et al., 2019).

Conclusions

Biological treatment has proven to be an effective option for managing RA in older adults, contributing to improved disease control and quality of life for this population. However, access in Peru is limited by multiple challenges, particularly economic, structural, and geographical.

Adopting strategies such as the incorporation of biosimilars, decentralization of medical care, and strengthening education and adherence programs for patients could significantly improve coverage and effectiveness of treatment in older adults. These actions would also help reduce the gap in access to innovative therapies, particularly in rural regions or areas with less healthcare infrastructure.

It is essential to promote deeper research on public policies in Peru aimed at identifying and overcoming barriers that hinder equitable access to biological treatments. Such studies should evaluate the efficacy of current health policies and propose new strategies tailored to the national context, including the successful experiences of other countries in utilizing biosimilars.

Finally, initiatives such as strengthening telemedicine and developing comprehensive care programs for older patients with comorbidities could represent substantial progress toward more equitable and efficient care. Implementing these strategies will contribute to improving the therapeutic approach to rheumatoid arthritis in Peruvian older adults, promoting their overall well-being and greater equity in the healthcare system.

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