REVIEW

Comprehensive Insights into the Economic Burden of Rheumatoid Arthritis in Latin America: A Systematic Literature Review of Regional Perspectives

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Purpose: Rheumatoid arthritis (RA) affects approximately 0.3 to 1.2% of the world's population. The objective of this study was to identify the existing literature on economic evaluations of RA in Latin America.

Patients and Methods: Studies of economic evaluations of patients with RA from 2000 to 2023 were analyzed using the databases PubMed, Scopus, Web of Science, Embase, Cochrane, and the Virtual Health Library following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Study quality was assessed using the Joanna Briggs Institute (JBI) tool, and qualitative analysis was done (following SwiM guidelines).

Results: A total of 851 articles were identified. Following the application of inclusion criteria to titles and abstracts, 117 articles were initially considered eligible. Of these, 42 were excluded due to population or outcome-based errors, leaving 27 articles and 48 abstracts for analysis. Duplicates were removed prior to this process. The included studies involved various designs: cross-sectional, longitudinal, prospective, and retrospective. Brazil accounted for the highest proportion of publications (33.3%), followed by Colombia and Mexico, each contributing 26%. Most economic studies focused on cost analysis (86%), while cost-effectiveness studies and cost-utility studies represented 7.4% and 3.3%, respectively. Predominant perspectives included third-party payer 26%, insurers 14.8%, social providers 7.4%, and mixed providers 3.7%. In terms of publications of abstracts, Colombia leaded at 35.4%. The predominant perspective was that of the provider 66.6%, including the general perspective (37.5%), private (34.3%), public (22%), and mixed (6.2%) and the perspective of third-party payers (33.3%).

Conclusion: Economic evaluations of rheumatoid arthritis in Latin America remain limited, with most studies focusing on cost analysis. Brazil, Colombia, and Mexico lead in publications, primarily from a provider perspective. Greater emphasis on cost-effectiveness and broader economic evaluations is needed to guide health policy in the region.

Keywords: economic burden, Latin America, rheumatoid arthritis

Introduction

The success of a health system is closely related to the type and risk of diseases present in a population, which directly impacts health care expenditure (HCE). Defined by the OECD (Organization for Economic Cooperation and Development), HCE represents the total resources allocated to health care goods and services, including treatment, rehabilitation, medical services, equipment, public health, and system administration. [1]

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High HCE is particularly evident in the case of high-cost or in some countries also known as catastrophic diseases. These diseases, as defined by the Pan American Health Organization (PAHO), are characterized by high costs, severe health impacts, and unsustainable household financing. Examples include chronic non-communicable diseases such as cancer, chronic kidney disease, and autoimmune diseases, which account for a significant portion of health care resources and impose a substantial financial burden on governments, health systems, and households.[2] Among autoimmune diseases, rheumatoid arthritis (RA) stands out due to its significant impact on functional abilities of individuals and health systems. Affecting approximately 1% of the population, predominantly women, RA requires specialized treatment and generates considerable economic and social costs.[3,4] These include direct medical expenses, labor-related costs (absenteeism, presenteeism, and unemployment), and broader social costs that challenge the sustainability of health and economic systems.[5]

A key measure to assess the burden of disease is disability-adjusted life years (DALYs), which quantify the years lost due to disability, illness, or premature death. In 2019, DALYs for RA in Latin America were highest in Mexico (0.30%), followed by Venezuela (0.24%), Colombia (0.21%), and Brazil and Argentina (both at 0.16%).[6,7] The disease's burden is compounded by comorbidities such as osteoporosis, hypertension, dyslipidemia, Sjögren's syndrome, diabetes, renal disease, and cardiovascular disease, which significantly increase the cost of care[8.] It is common for a small percentage of the population to consume most of the available resources, in other words, 20 to 30% of the population may use 70% of the resources expended.[9]

The financial impact of RA is amplified by the introduction of costly pharmacological treatments, particularly biological drugs. While these drugs have improved disease management, they have substantially increased direct medical costs, including hospitalizations, outpatient visits and surgeries. In countries like Brazil, Argentina, Mexico, and Colombia, approximately 65% of HCE for RA is attributed to direct medical and non-medical costs, while indirect costs account for about 30%. These expenses can represent up to 50% of household income and tend to rise as the disease progresses[7].

Socioeconomic disparities and differences in healthcare systems across regions significantly impact the economic burden of RA. The shortage of rheumatologists, particularly in rural areas, and the lack of primary care referral systems hinder early diagnosis and treatment.[10] Additionally, limited access to conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) and the low coverage of biological drugs (less than 10% in half of the countries) in public healthcare systems exacerbate the situation[10]. Factors such as low socioeconomic status and cultural barriers in rural and indigenous communities further restrict access to adequate care, increasing disability and worsening health outcomes.[11]

While studies on the economic evaluation of RA exist in Latin America and the Caribbean, the evidence remains limited, with most focusing primarily on direct and/or indirect costs. This highlights the need for more comprehensive economic evaluations to better understand the impact of RA in the region. Given the fragmented nature of the available literature and the lack of a complete synthesis, this study aims to conduct a systematic review to identify and analyze the main economic evaluations of RA in Latin America from 2000 to 2023, contributing to the knowledge base and informing public health decision-making.

Material and Methods

Search Strategy

This systematic review was registered in PROSPERO (Registration number: CRD42023459439). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed with no language limitations. The search strategy was done using the Patient, Intervention, Comparison, and Outcome (PICO) framework. All of the articles published in the PUBMED - SCOPUS - EMBASE - Cochrane Library - Web of Science and Virtual Health Library (VHL) databases from January 1, 2000, to December 31, 2023 were identified. (Supplementary data 1).

Selection Criteria

All studies involving economic evaluations of RA or direct costs that met the following inclusion criteria were included: 1. Case-control studies, cross-sectional or analytical prevalence design, cohort studies, controlled clinical trials ("CCT"), preclinical trials, simulation-modeling studies, conference abstracts, conference summaries, nursing clinic costing

studies. 2. Studies of the populations of Latin American countries belonging to the Economic Commission for the Americas and the Caribbean (CELAC): Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Colombia, Costa Rica, Cuba, Chile, Dominica, Dominican Republic, Ecuador, Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, St. Kitts and Nevis, St. Vincent and the Grenadines, St. Lucia, Suriname, Trinidad and Tobago, Uruguay, and Venezuela. Brazil is included because it is a Latin American power.

Exclusion Criteria: 1. Letters to the editor, systematic or narrative reviews, case reports, or case series. 2. Studies that included patients with Juvenile Arthritis.

Article Selection

Using the Rayyan application, all searches were imported from the databases.[12] Duplicates were subsequently removed; the studies were reviewed by title and abstract and were included or excluded based on the inclusion criteria. The articles were divided into 2 sections. They were distributed between 2 pairs of authors who reviewed the two sections initially by title and abstract. After that they exchanged sections to review the full text of those eligible in search of further data. Inconsistencies were resolved for each pair of reviewers by a third reviewer who led a joint review and helped reach a consensus.

Quality Assessment

The quality of the studies was evaluated using the "The Joanna Briggs Institute (JBI) Critical Appraisal tools for use in Systematic Reviews Checklist tool.[13] Four reviewers working in pairs used the JBI checklist that consists of 11 questions to investigate the methodological quality of economic studies. Each question was assigned a "yes", "no" or "unclear" weighting. Each pair of reviewers evaluated the articles and conference abstracts. Disagreements were resolved through a joint review with a third reviewer. The score limits for the methodological quality of the studies and conference abstracts were defined as a total score > 6 with all studies being considered. Agreement levels were evaluated by calculating the mean difference and standard deviation. What was evident in both cases was that the ratings of the different reviewers tended to be clustered near the mean. (Supplementary data 2 and 3).

Analysis

To condense the information, doing a synthesis without meta-analysis was proposed as a qualitative analysis of the data and not a quantitative analysis given the heterogeneity of all the articles by following the SWIM "Synthesis without meta-analysis" guide.[14] General and specific tables were established for reporting the information, and the data was recorded in Word and Excel. The results of the costs of the selected articles and abstracts were converted into US dollars as of 2023 using the exchange rates representative of the year of each study and the year-to-year values of inflation up to 2023. This was done by creating tables using Excel formulas for each country. (Supplementary data 4).

Ethics Approval and Informed Consent

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Research Ethics Committee on Human Beings, Fundación Universitaria de Ciencias de la Salud – FUCS, Bogota, Colombia (Record 0317–2021, June 1st, 2021). In Colombia, this study does not require any informed consent, because there is no patient contact, and it is considered without risk. Therefore, it does not require informed consent. Nevertheless, an authorization for the use and analysis of the data was taken from each patient.

Results

The search strategy identified 851 articles. After these initially selected studies were reviewed, duplicates were eliminated, and they were checked for compliance with inclusion criteria, 117 articles were considered eligible for the study. Of these, 42 were eliminated because they corresponded to the wrong population or outcome thus leaving a total of 27 articles[15–41] and 48[42–88] conference abstracts included which we decided to evaluate in order to do the proposed qualitative analysis. (Figure 1).
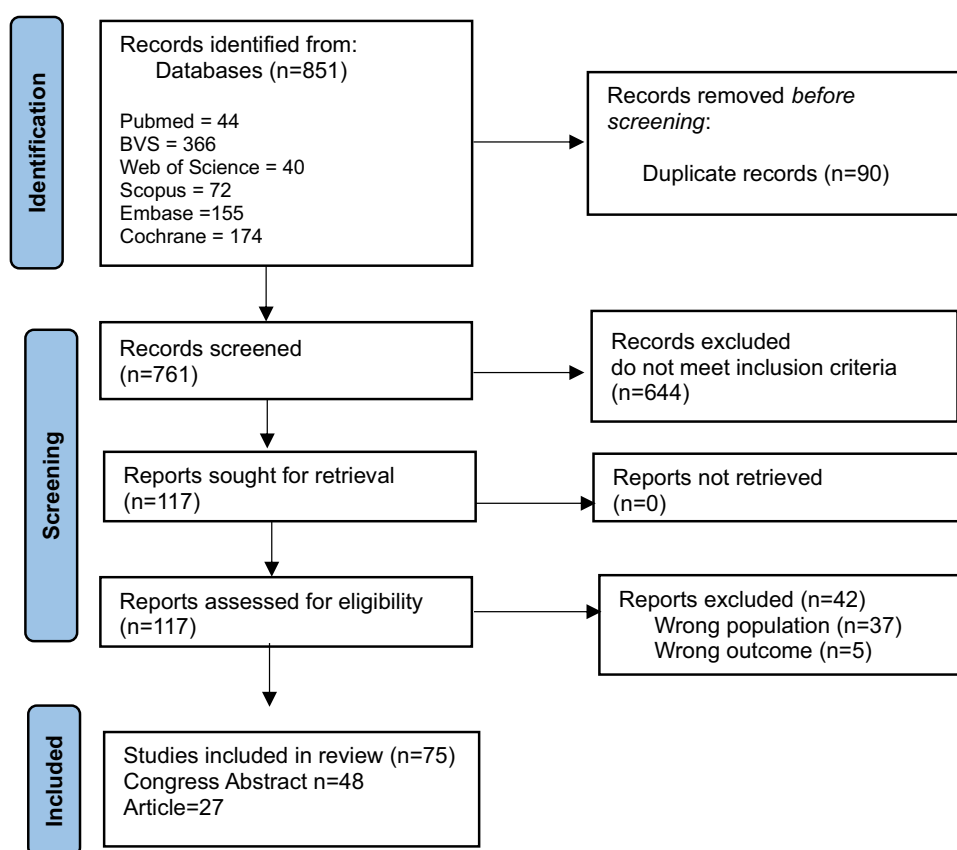
Figure 1 Identification of studies via databases and registries.

General Characteristics of the Articles

Of the 27 articles reviewed, there is a yearly publication frequency starting in 2003. The years which the most publications were reported in 2008, 2011, 2021, and 2023. The distribution of articles published by country gives the highest number of articles to Brazil with nine, followed by Colombia and Mexico with seven each. Three articles were found to have been published by countries collaborating with each other. The first was published jointly by Brazil, Mexico, Colombia, and Argentina. The second was published by Mexico and Puerto Rico and the third was a study by the BRICS countries (Brazil, Russia, China, India and South Africa) while Argentina reported a single article of its own. Regarding the population characteristics, the age range in which the studies were carried out was adults between 45 and 60 years of age. With respect to gender, the majority of the articles published related to women. Regarding the time horizon, which refers to the number of years over which resource consumption was quantified, these studies found a range between 1 and 27 years. Regarding study design, cross-sectional, longitudinal, prospective and retrospective studies were found. The perspective from which the economic evaluations were made was from that of the third-party payer 26%, from the insurer 14.8%, from the social perspective 7.4%, and from mixed providers 3.7%. The rest did not report. Inclusion criteria included: adults of both sexes who were in the official databases of each of the countries or provider entities. Moreover, only one article was found that reported the use of 13 clinical trials. The predominant economic evaluation is cost analysis 86%, followed by cost-effectiveness studies (CE) 7.4%, and cost-utility (CU) with 3.3%; 3.3% did not report. (Table 1).

Description of Findings by Country with the Most Published Articles (Table 2)
Brazil

These articles are written by a variety of authors. There is no single author who stands out in the frequency of their writing. Of the articles selected, 44.4% report the perspective from which the analysis was done the third-party payer's perspective accounted for 22.2% while another 22.2% focused on the insurer's perspective. In relation to the sources of

Table 1 General Characteristics of Included Articles

Authors	Year of Publication	Country	No. Population (% sex)	Mean Age in Years (SD)	Time Horizon	Study Design Type	Evaluation Year	Inclusion Criteria / Comments
Michaud et al, 2003.[15]	2003	USA [a]	150 77% F 23% M	61,7 (±13,1)	3 years	Longitudinal	1999–2001	Patients from the National Rheumatic Disease Data Bank who completed 2 of 6 semiannual questionnaires (1999–2001).
Pineda-Tamayo et al, 2004.[16]	2004	Colombia	41 71% F	45,2 (± 14.70)	6 years	NR	1999–2005	Patients attended at the Rheumatology Unit of the Clínica Universitaria Bolivariana 1999–2003.
Pineda-Tamayo et al, 2005.[17]	2005	Colombia	NR	NR	12 months	NR	2003	Five health services in Medellin city with rheumatology services.
Hernández-Cruz et al, 2006.[18]	2006	Mexico	90 92% F 8% M	43,2 (±14,2)	12 months	Descriptive	2005	< 18 years old and <= 80 years oldWith functional class I–II SteinbrokerActive disease (3 or more of: morning stiffness ≥ 60 minutes; ≥ 9 tender joints, ≥ 6 swollen joints, ESR ≥ 30 mm.
Chermont et al, 2008.[19]	2008	Brazil	100 92% F 8% M	51	3 years	Descriptive - retrospective	2001–2003	Patients with 1 year of follow-up in outpatient clinics
De Azevedo et al, 2008.[20]	2008	Brazil	192	47,7	2 years	Cross-sectional	2004–2005	Patients from the rheumatology division of the Federal University of Sao Paulo, aged 18–65 years, in work situation affected by RA.
Monterio et al, 2008.[21]	2008	Brazil	NR	NR	1–2 months	Observational - descriptive - prospective	NR	> 18 years of age of both sexes, at any stage of treatment
Mould-Quevedo et al, 2008.[22]	2008	Mexico	694 36%	46 (±14.7)	2 years	Cross-sectional	2004–2005	Patients who met diagnostic criteria and attended rheumatology services in various second and third level hospitals, as well as private consultations of investigators.
Mora et al, 2009.[23]	2009	Colombia	NR	NR	12 months	NR	2007	First year of RA diagnosis, affiliated to the health system of the Military Forces and treated at the Central Military Hospital.
Aceves-Avila et al, 2011.[24]	2011	México	381 292	NR	6 months	NR	2008–2009	NR

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Table 1 (Continued).

Authors	Year of Publication	Country	No. Population (% sex)	Mean Age in Years (SD)	Time Horizon	Study Design Type	Evaluation Year	Inclusion Criteria / Comments
Rojas et al, 2011.[25]	2011	Mexico	1000	39–64	5-year start adjusted to 10 years	NR	NR	Simulation in a hypothetical cohort of patients in three therapy arms and treatment sequence with RA and moderate to severe activity who have IR to MTX in management with ABA and two treatment arms with a fixed treatment sequence.
Quintana et al, 2011.[26]	2011	Colombia	NR	NR	2 years	NR	NR	Markov model design from literature search on measures of effectiveness, safety and utility of biologic therapy (INF, ETA, ADA).
Álvarez – Hernández et al, 2012.[27]	2012	Mexico	262	42,7	3 years	Cohort-nested cross-sectional multicenter study	2003–2005	>18 years old attending 11 institutional and private centers in five cities.
Bagatini et al, 2013.[28]	2013	Brazil	103 89% F 11% M	> 50 (70,9%)	2 years	NR	2008–2009	> 18 years of age of both sexes at any stage of treatment.
Salinas-Escudero et al, 2013.[29]	2013	Mexico	NR	NR	12 months	NR	NR	Pharmacoeconomic decision analysis of different biologic therapies (ETA, INF, ADA, TCZ) in patients with moderate to severe RA with previous failure to any DMARD.
Costa et al, 2014.[30]	2014	Brazil	26228 historic cohort 81.4% F 18.6% M	40 a 59	3 years	NR	2003–2006	Patients admitted between 2003–2006 treated with various drugs (AZA, CsA, CQ, HCQ, INF, LFN and MTX) for various rheumatoid pathologies.
Tundia et al, 2016.[31]	2016	Argentina Brazil Colombia Mexico	NR	NR	10 years	NR	2012–2022	NR
Gomes et al, 2017.[32]	2017	Brazil	NR	NR	13 years	Time series-type with a cross-sectional survey	1996–2009	Adults of both sexes with primary diagnosis of RA.
Silva et al, 2018.[33]	2018	Brazil	11573 81.3% F 18.7% M	52	NR	Retrospective cohort	2008–2013	Patients registered in the SIA 2008–2013.

Liberman et al, 2019.[34]	2019	Argentina	233	50,6 (±11,9)	15 years	Observational, longitudinal, descriptive and retrospective.	2002–2016	Analysis of 13 clinical trials to estimate the real cost of treatment with marketed drugs on the market.
Barreto et al, 2021.[35]	2021	Brazil	338	52,07	5 years	Prospective	2013–2018	Use of at least two DMARD in patients with high or moderate disease activity after 6 months. They had not received DMARDb and were on first-line treatment.
Machado -Alba et al, 2021.[36]	2021	Colombia	588 88.1% F 11.9% M	57,3 (±12,5)	2 years	Descriptive - retrospective	2014–2018	>18 years with RA, unresponsive to DMARDc or having received only one DMARDb, started DMARDb or Tofacitinib in 2014 and taking it more than 6 months.
Santos-Moreno et al, 2021.[37]	2021	Colombia	440 81% F 19% M	58 (±12,3)	2 years	Retrospective	2016–2017	< 18 years old with a presumptive diagnosis of seronegative RA. Negative results for RF biomarkers and ACPA but with EULAR 2010 diagnostic criteria.
Santos-Moreno et al, 2021.[38]	2021	Colombia	968 80.2% F 19.8% M	64	1 year	Prospective	2017	Patients treated at center of excellence.
Mendoza-Gutierrez et al, 2023.[39]	2023	Mexico	7050 81.2% F 18.8% M	50 a 69	2 years	NR	2016–2017	Patients treated at the Mexican Social Security Institute.
Mega et al, 2023.[40]	2023	Brazil	NR	NR	5 years	Descriptive - cross-sectional	2012–2017	Patients registered in the SIA database
Zhang et al, 2023.[41]	2023	Brazil Russia China India South Africa	NR	NR	27 years	NR	1990–2019	Patients registered in the database of the Institute for health metrics and evaluation of the University of Washington.

Notes: [a] Population from Mexico and Puerto Rico was taken from a total of 7527 included in the study.
Abbreviations: ABA, Abatacept; ACPA, Anti-citrullinated protein antibodies; AZA, Azathioprine; CQ, Chloroquine; CsA, Cyclosporine; DMARD, Disease Modifying Antirheumatic Drugs; DMARDb, Biologic Disease Modifying Antirheumatic Drugs; DMARDc, Conventional Disease Modifying Antirheumatic Drugs; F, Female; HCQ, Hydroxychloroquine; INF, Infliximab; IR, Inadequate Response; LFN, Leflunomide; M, Male; MTX, Methotrexate; NR, Not Reported; RA, Rheumatoid Arthritis; RF, Rheumatoid Factor; SD, Standard Deviation; SIA, Outpatient Information System.

Table 2 Specific Characteristics in Economic Evaluations of the Brazilian and Colombian Articles

Authors	Year Publication	Country	Perspective [a]	Data Collection [b]	Methods	Interventions	Exchange Rate	Sensitivity Analysis	Results
Chermont et al, 2008[19]	2008	Brazil	NR	Survey SF36 Questionnaire HAQ Questionnaire	Means, standard deviations and percentages; annual values per patient were used to discriminate resources.	None	Brazilian reals converted to USD in 2002 (R$1 = US $0.34)	NR	Average annual drug cost was $161.36 USD/patient and associated disease cost was $87.93 USD/patient. Average direct cost per patient was $370.36 USD/year and the average direct non-medical cost was $32.68.
De Azevedo et al, 2008[20]	2008	Brazil	NR	Systemic Structured Interview Questionnaire SF36 Questionnaire HAQ Questionnaire	Linear regression models	None	NR	Direct cost per patient in reals converted to the equivalent minimum wage using the minimum wage at interview, a step necessitated by economic conditions. Variations in indirect cost estimates were evaluated from individual and population data.	Indirect costs according to employment status are $211,172.56 for retirees is $ 4493.03, for workers 9055.24 and for each $109.09. The estimated indirect costs per patient per year are 56% of the national income product per capita estimated from 2004 and 2005 per capita prices in Brazil ($4284 and $4320 USD respectively).
Monterito & Zanini, 2008[21]	2008	Brazil	Third Payer	Initial survey Medical records Dispensing records	Analytical decision making model based on the Markov models	ADA, INF, ETA and LFN	NR	It was performed through the change of variables, varied the percentage effectiveness of MTX, using the response values to reach the ACR index of 45, 50 and 55%, the variation in the effectiveness of INF to 62% when MTX is 45%.	The cost of the treatment stages was R$ 683.40 (Cycle c 1) (382 USD), R$ 2788.44 (Cycle 2 (1561 USD)), R$ 3262.65 (Cycle 3) (1826 USD), R$ 3839.25 (Cycle 4) (2149.8 USD), R$ 53,898.70 (Cycle 5)(30182 USD).
Bagatini et al, 2013.[28]	2013	Brazil	NR	Initial survey Medical history Dispensing records	Micro costing	None	NR	NR	Direct medical cost of R $2,045,596.55 ($981,886 USD), with an average of R $19,860.16 per year/patient ($9532 USD). The health system covered 73.6% of the total. Of the total, 90.8% was for the purchase of medicines, 2.5% for hospitalizations, 2.2% for complementary examinations and 2.1% for medical consultations. Total expenditure on drugs was R$1,875,178.99. Therapeutic costs were R $15,450.37, complementary examinations were R$45,974.24, with an average of R$6.40 per laboratory test.

Costa et al, 2014[30]	2014	Brazil	Insurer	National Drug User Database	Probabilistic deterministic matching	None	NR	NR	Expenditure was higher in > 50 years who used DMARDs, with INF expenditures were higher in young people, without being representative changes. The higher expenses were due to complications, there were higher averages in the group that used DMARDs for other arthritis (R $155.53 ± 111.23; R$158.82), rheumatoid nodule (R$231.79 ± R$314.05; R$146.41). Felty's syndrome had more expenses (47.9%) and 34.5% for unspecified seropositive RA (20.8% and 34.3%).
Gomes et al, 2017[32]	2017	Brazil	NR	Inpatient and outpatient health information system database	Linear regression models	None	NR	NR	Total management costs amounted to R$26,659,127.20 (US$ 7,979,738). There were 7691 hospitalizations, (28%) of the total cost. 6000 for clinical procedures, totaling a cost of R$ 1,144,402.08 (15%) of the hospital expense. In outpatient management, high-cost procedures for pharmacological treatment are R$ 40,188, contributing R$ 19,446,628.75 (5,833,988 USD).
Silva et al, 2018[33]	2018	Brazil	Insurer	Ambulatory health information system database	Multiple linear and bivariate linear regression analysis, with probabilistic matching	ADA, ETA, INF, MTX, AZA, CsA, CQ, HCQ, LFN, SSZ.	Values adjusted to the 2015 inflation index	NR	Average monthly expenses for ADA were $2333.59, ETA $ 4434.76, INF $ 2138.72, MTX $ 21.22.
Barreto et al, 2021.[35]	2021	Brazil	Third Payer	EQ5D Survey	Markov model with 6-month cycles	ADA 198 (58, 8%) ETA 94 (27,81%) GOL 46 (13,61%)	5% recommended by the Economic Health Assessment Guidelines	The change in costs for discontinuing GOL affected the choice between drugs, favoring ADA. GOL was more cost effective (75%) at one GDP per capita and over 60% for three GDP per capita.	GOL's cost was $30,480.69 USD and profit was $5607 lower costs with lower cost-utility ratio. ETA $33,458.42 had a profit of $5578, with lower profit and higher cost than GOL. ADA $35,615 and profit of $5661, with incremental cost utility ratio of $95,095.35 compared to GOL in 5 years of follow-up.

(Continued)

Table 2 (Continued).

Authors	Year Publication	Country	Perspective [a]	Data Collection [b]	Methods	Interventions	Exchange Rate	Sensitivity Analysis	Results
Mega et al, 2023[40]	2023	Brazil	NR	Ambulatory health information system database	Absolute and mean frequencies to mean values	ABA – ADA- CZP – ETA – GOL – INF -RTX - TCZ	Brazilian reals converted to USD in 2017 (1BRL = 0.302 USD)	NR	Spending of US$500 million on the acquisition of 2 million units of biologic drugs during the period. ADA 40 mg and ETA 50 mg had the greatest impact on financial spending, accounting for 68.3% of biologic drug expenditures. The average annual expenditure was $93 million. RA with rheumatoid factor accounted for 45.5% of expenditures, followed by RA without rheumatoid factor with 22.5%.
Zhang et al[41]	2023	Brazil [d]	NR	Institute for health metrics and evaluation Database Washington University	Joinpoint regression model	NR	NR	NR	The DALY rate in 2019 was 5.3% higher than in the 1990s (40.33 cases per-100,000 population). An increasing age trend was observed, indicating that the DALY burden tends to be higher in older age groups. In the period 1994 and 2019, the relative risks increased over time.
Pineda-Tamayo et al, 2004[16]	2004	Colombia	Third Payer	Medical records Data from the Statistics Department and the Cost Department of the Clinica Universitaria Bolivariana Medellín.	Percentages and measures of central tendency were used to describe clinical and demographic variables and hospital costs.	None	Data obtained in COP, adjusted according to CPI and converted to USD as of September 2003.	NR	Organ damage due to RA caused 60% of the hospitalizations. Medications and medical-surgical material were the highest costs, while medical fees were 3%. Cardiovascular diseases significantly affected hospital costs, while the number of morbidities did not show a significant impact.
Pineda-Tamayo et al, 2005[17]	2005	Colombia	Societal perspective	Questionnaires to pharmacies Price records for each consultation and intervention	Hypothetical model of RA patients in the first year of disease, projecting costs.	Model of early intervention that included 4 therapeutic schemes	Representative dollar rate as of September 30, 2003 (2861.6 COP per dollar).	NR	The total costs of medical intervention in early RA in the different therapeutic schemes Scheme 1. US$728, scheme 2. US$779.3, scheme 3. US$860.9 scheme 4. US$1383.2; costs of laboratory tests among the 5 institutions vary from US$76 to US$204.

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Mora et al, 2009[23]	2009	Colombia	Third Payer	Databases with cost history	Simulation of RA and classification into three categories according to disease activity, based on the DAS28.	DAS28 < 3.2 received meloxicam and a combination of two DMARDs: MTX with HCQ, LFN with HCQ, SSZ with HCQ or LFN with HCQ. DAS28 between 3.2 and 5.1 controls in Rheumatology every six weeks for three months, then every two months, along with follow-up exams and meloxicam. DAS28 > 5.1 were followed up in Rheumatology every six weeks for three months, then every two months, with meloxicam, MTX and an anti-TNF treatment. Follow-up examinations were performed at the same interval.	Costs obtained in COP, converted to USD, according to the representative market rate as of January 28, 2008 (COP 1969.95 per dollar).	NR	The management of RA varies according to its activity: mild ($3'325,796), moderate ($3'554,193) and severe ($46'155,596) in the first year. 86% of the total cost is for drugs, 10% for laboratories and 4% for medical care. Direct costs range from $1689 to $1805 with conventional treatments with disease modifiers, $23,441 with anti-TNF in the first year.
Quintana et al, 2011[26]	2011	Colombia	Third Payer	A total of 2599 references were reviewed in the literature up to August 2010. Pivot studies such as ATTRACT for INF, ARMADA for ADA and TEMPO for ETA were included, in addition to other clinical variables obtained mainly from RA patient registries.	Markov models with quarterly cycles and 4 states; this model was derived from 19 records, from 12 countries, with information on more than 30,000 patients.	ADA, ETA or INF	Annual discount rates of 3% for both costs and QUALY Given in COP	The analysis focuses on matching the monthly costs between ADA and ETA due to their similar effectiveness and safety. If the monthly cost of INF is considered, to match it with ADA it should be $2.55 million and to match it with ETA it would be $2.25 million per month. If the overall costs are equal, the other therapeutic alternatives are preferred over INF, as they are slightly more effective and safer.	INF is not as recommended in our model due to cost, dose adjustments and high dropout rate and a less favorable safety profile. For Colombian patients with RA, ATS appears to be more beneficial than INF, with lower total cost and higher effectiveness. It is also more cost-effective than ADA, offering similar effectiveness at a lower total cost. Estimated costs are: ADA 40 mg every 2 weeks $3,420,000, ETA 50 mg per week $3,230,000, INF 3 mg per-kg every 8 weeks (70 kg weight) $2,827,000. Costs for severe adverse events are estimated at $5,000,000, and for mild events, $500,000.

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Table 2 (Continued).

Authors	Year Publication	Country	Perspective [a]	Data Collection [b]	Methods	Interventions	Exchange Rate	Sensitivity Analysis	Results
Machado-Alba et al, 2021[36]	2021	Colombia	NR	Medical records	Macro costing	Patients subjected to DMARDb and DMARDc	COP with conversion to USD at the respective exchange rate according to the Banco de la Republica 1 USD=2920 COP (December 2017).	NR	Average annual costs per patient ($8996.9 ± 2172). Total expenditure in 588 patients ($5,257,256). 97.2% of the total cost went to pharmaceutical expenses, 92.1% directed to DMARDb or tofacitinib. The remaining costs involved DMARDc, analgesics and other drugs (1.7%) for subcutaneous applications or infusions and 1.1% for medical visits.
Santos-Moreno et al, 2021[37]	2021	Colombia	Third Payer	Medical records	Cost analysis in two scenarios 1. Conventional arthritis diagnosis 2. Alternative diagnosis	None	Costs expressed in 2017 prices and converted to USD, using the average exchange rate for 2017 (1 USD= $ 2951 30 COP).	NR	Conventional diagnostics totaled $59.20 USD, 27% for rheumatology consultations. The alternative diagnostic approach cost $269.57, mainly for imaging techniques. Follow-up of a seronegative patient for one year cost $5419.3, with drug treatment being the largest expense: $5332.6 (98.4% of the total cost).
Santos-Moreno et al, 2021[36]	2021	Colombia	Third Payer	Medical records	Cost analysis according to the Economic Evaluation Guide of the Instituto de Evaluación de Tecnologías en Salud de Colombia	None	Costs expressed in USD using the exchange rate reported by Banco de la Republica for 2017.	NR	Treating 968 patients under the T2T strategy ensures significant savings: 36.5% in the first year, saving US$231.3 per patient. This amount represents 87.4% of the minimum monthly salary for 2018. With this comprehensive care, a reduction in healthcare costs and an increase in the number of patients in remission or with low disease activity is achieved.

Notes: [a] (society, third payer, provider, patient and family), [b] Basis, surveys, questionnaires, application of simulation models: (Markov, decision tree, among others), [c] RA treatment cycles, [d] Includes the emerging countries that form the BRICS group (Russia, India, China, South Africa and Brazil). Regarding the type or model of evaluation used, all the studies were on cost analysis, only one was on cost-utility.[8]

Abbreviations: ABA, Abatacept; ADA, Adalimumab; Anti-TNF, tumor necrosis factor inhibitor; AZA, Azathioprine; CPI, consumer price index; COP, Colombian pesos; CQ, Chloroquine; CZP, Certolizumab CsA, Cyclosporine; DAS28, Disease Activity Score; DALY, Disability Adjusted Life Years; DMARD, Disease Modifying Antirheumatic Drugs; DMARDs, Synthetic Disease Modifying Synthetic Drugs; DMARDb, Biologic Disease Modifying Antirheumatic Drugs; DMARDc, Conventional Disease-Modifying Antirheumatic Drugs; EQ5D, EuroQol-5D ETA, Etanercept; GDP, Gross domestic product; GOL, Golimumab; HAQ-DI, Health Assessment Questionnaire – Disability Index; HCQ, Hidroxichloroquine; INF, Infliximab; LFN, Leflunomide; MTX, Methotrexate; QALY, Quality of Life Adjusted Life Year; RA, Rheumatoid arthritis; RTX, Rituximab; SSZ, Sulfasalazine; T2T, Treat to target; TCZ, Tocilizumab; USD, United States dollar; NR, No reported.

information, 66.6% obtained it through the application of surveys and SF-36 questionnaires on Health Status (Short-Form) and HAQ *(Health Assessment Questionnaire)*. The other 33.4% use the national database of the hospital and outpatient health information system. Regarding the type of analysis, 100% were found to use linear and logistic regression measurements with probabilistic matching. As for evaluation methodologies, 22.2% used decision tree, and Markov models while only 11.1% applied micro-costing methodologies. In terms of intervention technology, 44.5% reported using Biologic DMARDS (bDMARDs) among which the most frequent were anti-tumor necrosis factor (Anti-TNF) agents: Adalimumab (ADA), Infliximab (INF), Etanercept (ETA). Cost analysis, in turn, was the predominant method in 88.8% of the articles. A sensitivity analysis was done under certain specific conditions in 33.3% of the studies to assess the values of independent variables attributable to a dependent variable. Of these, 22.2% identified changes in the percentage effectiveness of Methotrexate (MTX) and changes in cost-effectiveness when Golimumab (GOL) was applied. Another 11.1%, given the country's economic situation, estimated the indirect cost based on individual and population data. The remaining 66.7% did not report any sensitivity analysis.

The results, in turn, were calculated with the exchange rates presented by the articles and brought forward to the year 2023 while factoring in the country's annual inflation. The average annual cost of RA medication for 2002 was US $161.36 dollars/patient, the average direct cost per patient was US$370.36 dollars/year, and the average direct non-medical cost was US$32.68 dollars.[19] As of November 2023, the annual cost of RA medication was US$921.85 dollars/patient, the average direct cost per patient was US$2115.34 dollars/year, and the average direct non-medical cost was US $190.92 dollars. A study in 2008 reported, with a time horizon of 1 year, the cost based on a model of treatment cycles in line with the medication used and the transition time between each cycle as follows: US$382 (cycle 1), US$1561 (cycle 2), US$1826 (cycle 3), US$2149.8 (cycle 4), US$30,182 (cycle 5).[21] These values would have been US$2639.03 (cycle 1), US$10,784.09 (cycle 2), US$12,614.82 (cycle 3), US$14,851.7 (cycle 4), US$20,8510.76 (cycle 5) as of 2023. Another study mentioned that the direct medical cost in 2013 was $981,886 which is equivalent to an average of $9532 dollars per patient/year with a time horizon of 2 years.[28] This value in direct medical costs would be US$4,518,198.25 as of 2023, which is equivalent to an average of US$43,862.05 dollars per patient/year. The total expenditure for inpatient and outpatient medical treatment of RA with a time horizon of 5 years was reported to be $7,979,738 in 2016.[20] As of 2023, this cost could have amounted to US$17,724,939.4. Last of all, the cost of GOL in 2021 was US$30,480.69 of ETA US$33,458.42, and of ADA US$35,615 over a 5-year follow-up period. This was based on maintaining similar profitability but differences in cost. This impacted the economic model due to the prices agreed upon with the manufacturers and affected the incremental profit for them.[35] The cost of GOL in 2023 would have been US$30,662.18, ETA US $33,657, and ADA US$35,827.9 for 5 years of follow-up while maintaining a similar profit. A 2023 article mentioned that ADA 40 mg and ETA 50 mg had the greatest impact on financial expenditure since they accounted for 68.3% of the expenditures on biological drugs. The average annual expenditure was US$93 million. RA, with seropositive rheumatoid factor accounted for 45.5% of the expenditures, followed by RA with seronegative rheumatoid factor at 22.5%.[40]

Therefore, in Brazil, the direct medical cost of RA treatment would probably range from US$2115.34 dollars per patient/year to US$43,862 dollars per patient/year, depending on the phase of treatment the patient is in and bearing in mind the fact that Brazil is considered the country with the second most depreciated currency in Latin America for 2023.

Colombia

Between (Santos-Moreno) and (Quintana G) there is a tie for first place in publications, corresponding to 66.6%. A total of 85.7% of the articles written in Colombia report the perspective from which the analysis was carried out. Thus, this country is the one that most frequently reports this data. Ninety-six percent do so from a third-party payer perspective and 4% from a social perspective. Seventy-one percent used medical records as a source of information and the rest used historical cost databases. As for the method of analysis, 71% used scenario simulations by means of Markov models. Another 14.5%, in turn, used the macro-costing methodology. The other 14.5% followed the recommendations of the Economic Evaluation Guide issued by the Colombian Institute for Health Technology Assessment (IETS in Spanish). Fifty percent of the articles mention procedures related to disease stage, bDMARDs, and csDMARDs. The evaluation that prevails in 100% of the studies is cost evaluations. Colombia as a country reports a sensitivity analysis less than any other at only 14.2% and does so when bDMARDs such as ADA, ETA or INF are used.

Thus, the results were calculated with the exchange rates presented by the articles and carried forward to the 2023 exchange rate while factoring in the country's annual inflation and highlighting the following: A study in 2004 reported the total costs of medical treatment of early RA in the different therapeutic approaches; Approach 1. US$728, Approach 2. US$779.3, Approach 3. US$860.9, Approach 4. US$1383.2; laboratory test costs among the 5 institutions range from US76 to US204.[16] The total costs of medical treatment of early RA for the different therapeutic approaches in the year 2023 would be as follows: Approach 1. US$1256.34, Approach 2. US$1344.87, Approach 3. US$1485.69, Approach 4. US$2387.05; laboratory test costs among the 5 institutions range from US$131.16 to US$352. The average cost of caring for a patient in the first year with mildly active disease in 2008 was US$1689, with moderate activity US$1805, and with [36] severe activity US$23,441 when using anti-TNF. 25 The average cost of caring for a patient in the first year with a mildly active disease in 2023 would have been US$1529, with moderate activity US$1634.05, and with severe activity US$21,220 when using anti-TNF.[23] Costs in 2017 were found to average US$8996.9 ± US$2172 per RA patient per year.[36] As of 2023, the annual average is likely to be US$8466.55 ± US$2044.17. Finally, a last study in 2021 reported that the total cost of conventional diagnosis in a patient with seronegative RA was estimated to be US$59.20 and that the cost of a proposed new alternative diagnostic model including more imaging was US$269.57. However, although the proposed diagnostic alternative is a priori five times more expensive, there is a savings in one-year treatment costs of US$1570.75520 due to ruling out RA in 74% of the cases using the new alternative. The cost, in turn, of treating a patient over one year of follow-up was US$5419.3 (range US$5125.8 - US$5787.7). However, the highest cost was related to pharmacological treatment (US$5332.6). Therefore, increasing the number of patients in remission and with low disease activity would result in a cost saving of US$223,874/year and US$231.3 per patient.[38] The total diagnostic cost as of 2023 would have been US$ 67.15. Follow-up for a seronegative patient could cost an average of US$ 6146.36. The pharmacological treatment was about US$ 6047.69. The savings in cost from the increase in the number of patients in remission and with low activity were about US$253.88 dollars/year and US$262.35 dollars/patient. In this regard, it is clear that the trend of inflation in 2021 had an impact on raising prices and, for previous years, there is evidence of a drop in prices due to low inflation.

Other Countries (Table 3)

Mexico

The authors of these articles are varied. There is no one author who predominates in the frequency of the writing of these articles. Only 42.8% of the selected articles report an analysis perspective. Of these, 28.5% correspond to the insurer's perspective and 14.36% to the provider's perspective. As for the sources of information, like Brazil, 71.4% are obtained from the application of surveys and HAQ questionnaires. The most commonly used data analysis models (57.1%) were decision trees and simulations of treatment therapies, 28.6% were clinical trials and cross-referencing of prescriptions with the way patients take their medications, and the remaining 14.3% corresponded to a macro-costing study based on DRGs (Diagnosis-Related Groups). Regarding treatment technologies, only 28.5% report using the same bDMARDs as Brazil (ADA, INF, ETA) and 14.3% (Clinical Trial) carried out a three-stage procedure. Cost analysis was the predominant method for 71.4% followed by CE studies (28.6%). Only 43% did a sensitivity analysis. Of these, 28.5% report sensitivity in the scenarios proposed and the other 14.3% report Abatacept (ABA) as the most cost-effective alternative with dominance over the other drugs.

With respect to the results, these were calculated with the exchange rates presented by the articles and brought forward to the year 2023 while factoring in the country's annual inflation. The total direct costs in 2005 were $152,704.11 dollars, $1735.27 per patient/year. The costs of medical care were US$78,386.43, US$890.75 per patient/year.[27] The total direct costs would have been US$204,001.7, US$2317.84 per patient/year, and the medical care costs would have been US$104,718.13, US$1188.98 per patient/year, as of 2023. The average treatment costs for patients treated with Tocilizumab (TCZ) in 2010 with a time horizon of 5 years were US$198,705, ADA US$188,534.45, INF US$175,838.79, ETA US$172,033.87, ABA US$169,263.20 and with Rituximab (RTX) US$97,373. Of these, ABA is the most cost-effective and would result in greater well-being for the population since each year of life gained, adjusted for quality of life, would cost US$86,375.43.[25] As of 2023 with a time horizon of 5 years, the treatment costs for patients treated with TCZ will probably be US$247,045.25; for those treated with ADA US$234,399.89; with INF, US

Table 3 Specific Characteristics in Economic Evaluations of Items From Mexico and Other Countries

Authors	Year Publication	Country	Perspective [b]	Data Collection [c]	Methods	Interventions	Exchange Rate	Sensitivity Analysis	Results
Hernández-Cruz et al, 2006[18]	2006	Mexico	NR	Structured questionnaire	Clinical trial with 48-week follow-up	**Scenario 1**: 4 visits per year, where paraclinical examinations were performed **Scenario 2**: 5 visits per year, with more detailed paraclinical analyses **Scenario 3**: Costs associated with drug trials.	NR	Costs decreased significantly in scenarios 1 and 2, when the third scenario was added, costs increased by $5218.8 USD and $59.3 per patient/year.	Total direct cost $152,704.11 USD in 2005, or $1735.27 patient/year. Medical care costs $78,386.43 USD in 2005, $890.75 patient/year. Medication costs of $39,339.5 USD and $447.04 per patient/year.
Mould-Quevedo et al, 2008[22]	2008	Mexico	NR	Coping questionnaires, functional capacity, disease activity, interviews, and clinical studies	Descriptive and analytical statistics were used to calculate the OOP in MXN, converting them to USD to estimate the real direct cost of treatment for each disease.	None	OOP calculated in MXN and converted to USD ($10.7 pesos per $1 USD, 2005)	The influence of health institutions other than IMSS would decrease direct medical costs to $1442.3. The reduction of direct medical costs in Mexico increases the OOP of the patient and family (25–30%) over the total annual cost.	The annual direct medical cost is $1724.2. 11% of the patients were hospitalized (average $246.6). Outpatient spending was 73.7% of the total. The direct cost was $2334.3 and $2289.4 respectively. The most common assistive devices were canes, crutches, wheelchairs, and walkers. 80.9% of patients used canes (average $12.6). 0.4% incurred expenses for third-party assistance, 0.8% received physical therapy and rehabilitation (average annual cost $672.9).
Rojas et al, 2011.[25]	2011	Mexico	Insurer	HAQ-DI	Birmingham model for RA with three arms	ABA versus other available biologic therapies used for the treatment of RA (ADA, ETA, INF, RTX and TCZ).	Discount rate of 11% for resources and 3.5% for health care	The analysis suggests that ABA is the most cost-effective option and outperforms other drugs, except RTX, which does not outperform ABA.	Average cost of care over 5 years: TCZ: $198,705, ADA: $188,534.45, ETA: $175,838.79, INF: $172,033.87, ABA: $169,263.20 and RTX: $97,373.95. RTX is less expensive over 5 years. The cost-effectiveness ratio shows that ABA is more efficient (cost of $86,375.43 per QALY).
Aceves-Avila et al, 2011[24]	2011	Mexico	NR	Semi-structured questionnaire	Cross-referencing of prescriptions with how patients take medications	None	NR	NR	Medication error was 43% by patient decision, 20.5% by primary care physicians, 6.5% by other physicians, and 40.2% by pharmacy errors. Sum does not add up to 100% due to multiple errors per patient in a month. Loss of 207 work days/patient with drug omission. Monthly wage losses of $10,764 and annual $129,168. Direct drug costs for a patient receiving CQ, MTX and high-dose diclofenac were $57.24 per month and $686.88 per year.

(Continued)

Table 3 (Continued).

Authors	Year Publication	Country	Perspective [b]	Data Collection [c]	Methods	Interventions	Exchange Rate	Sensitivity Analysis	Results
Álvarez – Hernández et al, 2012[27]	2012	Mexico	NR	HAQ-DI	Birmingham model for RAR with three arms	ABA versus other available biologic therapies used for the treatment of RA (ADA, ETA, INF, RTX and TCZ).	Discount rate of 11% for resources and 3.5% for health care	The analysis suggests that ABA is the most cost-effective option and outperforms other drugs, except RTX, which does not outperform ABA	Estimated annual cost ($3559 ± 6621) in direct expenses and ($1409 ± 4099) in indirect expenses. Per patient was $5534.8 USD, 65% direct costs and 35% indirect costs. Medications accounted for 29% of the total cost. There was a high unemployment rate both in 8 patients (61.5%) and their relatives in economically active years (44.4%).
Salinas-Escudero et al, 2013[29]	2013	Mexico	NR	Retrospective information from international research and the main direct costs of treatment in the Mexican health system.	Decision analysis model that represents the probable clinical evolution after different therapeutic options.	ETA INF + MTX ADA + MTX TCZ + MTX RTX + MTX	Costs in 2011 MXN and, given the one-year time frame, the usual 5% discount rate was not used for the requested costs and clinical outcomes.	NR	ETA was more cost-effective, with lower cost per case with successful response: $187,740.4 for ACR 20 and $476,525.8 for ACR 70: -$21,170.10 than ADA, -$4484.70 than INF and -$9064.05 than TCZ.
Mendoza-Gutierrez et al, 2023[39]	2023	Mexico	Insurer	Non-communicable disease analysis system databases. Medical statistics system -Datamart. DRG	Macro-costing with DRG generation	None	The exchange rate during the 2017 evaluation period was (1 USD= 18.7MXN).	NR	Laboratory and diagnostic tests represented 69.3% of the total costs in both years, in second place surgical procedures on the musculoskeletal system with 19.1% and 18.7% of the total costs and third physical therapies between 2.6% and 3.2%. The procedures performed in hospitalization were those on the musculoskeletal apparatus generating a cost of $132,053,692 MXN and $130,144,272 MXN followed by interventions on the cardiovascular apparatus with 11.8 million MXN 2016 and 2017 11.5 million MXN.

Liberman et al, 2019[34]	2019	Argentina	NR	Medical records	Clinical trial	13 clinical trials START7 IV (INF) AIM8 III ABA ATTEST9 III ABA RAPID10 III CZP GO BEFORE11 III GOL GO FORWARD12 III GOL ML 1938513 IV RTX 11 62 ALLOW14 III ABA ACQUIRE15 III ABA AMPLE16 III ABA BREVACTA17 III TCZ ENTRACTE18 IV TCZ TOZURA19 III TCZ	Estimated costs in Argentine pesos expressed in USD considering the exchange rate as of December 2016 ($15.83 Argentine pesos ¼ USD $ 1).	NR	Average annual cost per patient with DMARDb ($30,567.40), DMARDc ($104.90). Total savings in treatment of patients who participated in Phase IV clinical trials ($ 4,721,074.20) considering different values of DMARDb. The average annual cost per patient was estimated at $36,016.20 and DMARDs, ($ 81.70).
Tundia et al, 2016[31]	2016	Argentina Brazil Colombia Mexico	Social perspective	NR	Economic model with seven individual models	ABA, ADA, CZP, ETA, INF, RTX and TCZ	Brazilian reals, Argentine pesos, Colombian pesos, MXN, the discount rate of each country was used for the health technology evaluations to assess the overall return on investment.	NR	Projected net savings among patients for biologics 2012–2016. Cumulative savings of $2.352 billion Argentine pesos, $9.004 billion reals in Brazil, $728.577 billion Colombian pesos and $18.02 billion MXN.
Michaud et al, 2003[15]	2003	EEUU [a]	NR	SF36 EQ5D Questionnaires SF6D VAS Questionnaire	Monte Carlo simulations with 1000 repetitions	None	NR	RA costs vary by drug therapy. If the prevalence of biologic therapy were to increase to 40% with a 20% increase in costs, an annual direct medical cost of $12,616 is estimated, compared to $9519. If regulations and competitive constraints reduced use to 30%, decreasing costs by 20%, the annual cost would be reduced to $9032.	Total direct medical costs in 2001 ($9519), drug expenses (66%) of the total. Inpatient and outpatient hospital and procedure costs (17%) and 16% of total costs. Costs decrease with age in > 65 years at a rate of $72 per year. Duration of RA increased costs during the first 10 years at a rate of $47 per year.

Notes: [a] Population from Mexico and Puerto Rico was taken out of a total of 7527 included [b] Society, third payer, provider, patient and family, [c] Basis, surveys, questionnaires, application of simulation models: (Markov, decision tree, among others). Regarding the type or model of evaluation used, most of the studies were cost analysis studies, only two were cost-effectiveness studies.[6,8]

Abbreviations: ABA, Abatacept; ADA, Adalimumab; ACR, American College of Rheumatology; CQ, Chloroquine; CZP, Certolizumab; DMARD, Disease Modifying Antirheumatic Drugs; DMARDs, Synthetic Disease Modifying Synthetic Drugs; DMARDb, Biologic Disease Modifying Antirheumatic Drugs; DMARDc, Conventional Disease-Modifying Antirheumatic Drugs; DRG, Diagnosis-Related Group; EQ5D, EuroQol-5D ETA, Etanercept; GOL, Golimumab; HAQ-DI, Health Assessment Questionnaire – Disability Index; IMSS, Mexican Social Security Institute; INF, Infliximab; ISSSTE, Institute of Security and Social Services for State Workers; IV, Intravenous; MTX, Methotrexate; MXN, Mexican Pesos; OOP, Out-of-pocket expenses; QALY, Quality of Life Adjusted Life Year; RA, Rheumatoid arthritis; RTX, Rituximab; TCZ, Tocilizumab; USD, United States dollar; NR, No reported.

$218,615.25; with ETA, US$213,885.67; with ABA, US$210,440.71; and with RTX US$121,061.56. The quality-of-life-adjusted life year has a cost of US$107,388.01. And one last article from 2013 reported that treatment with ETA was more cost-effective because it presented the lowest cost per case with a successful response at a cost of $187,740 per patient which was the lowest associated cost for the treatment of RA: US$21,170.10 less than ADA, US$4484.70 less than INF and US$9064.05 less than TCZ.[29] In 2023 figures, the cost trend per patient with ETA would have been US$219,606.93 and US$24,763.39 less than the ADA, US$5240.43 less than the INF and US$10,602.52 less than the TCZ. Last of all, an article from 2023 mentions that laboratory and diagnostic tests accounted for 69.3% of the total costs over the two years of the study, followed by surgical procedures on the musculoskeletal system with 19.1% and 18.7% of the total costs, and physical therapy between 2.6% and the 3.2%.[39] This article did not include studies of drug costs.

Argentina

Only one article was identified for this country. The authors compiled 13 clinical trials where a cost evaluation was done with no economic perspective or sensitivity analysis reported. They conclude that the average annual cost per RA patient under treatment with bDMARDs in 2016 cost a total of US$30,567.40 while for csDMARDs it was US$104.90.[34] As of 2023, treatment with bDMARDs cost US$17,551.31, while for csDMARDs it was US$59.72. This drop in prices can be attributed to the depreciation of this country's currency, which ranks third in Latin America, as of 2023.

Cooperative Study (Brazil, Mexico, Colombia and Argentina)

Corresponds to a published article carried out in these countries. This is the only study that does the analysis from a social perspective. The method used to analyze the information were individual economic models. In all 4 countries, the same procedure was carried out with: ABA, ADA, Certolizumab Pegol (CZP), ETA, INF, RTX and TCZ. The evaluation carried out is a cost study. The research reviewed expanded use of bDMARDs products between 2012 and 2022 for RA patient resulted in a cumulative net cost savings of $2.351 billion Argentine pesos, $9.004 billion reals in Brazil, $728.577 billion Colombian pesos, $18.02 billion Mexican pesos by the year 2012.[31] Carried forward to the year 2023, the cumulative cost savings for each country would be: 5089 billion Argentine pesos, $8286 billion Brazilian reals, $3482 billion Colombian pesos, and $3789 billion Mexican pesos.

Mexico and Puerto Rico

This is a study that was done in the US, but it was based on a population from Mexico and Puerto Rico that lives in the US The source of information was HAQ questionnaires, a visual analog scale, and SF36. The analysis of the information was carried out by means of 1000 repetitions through a Monte Carlo simulation. The type of evaluation done was a cost evaluation. Sensitivity analysis was done with the prevalence of the use of biological therapy. The total direct medical cost of patients with RA in 2001 was US$9519[15.] Given the average US inflation rate for the last 22 years, which is reported to be 2.45%, the direct medical cost calculated for 2023 would be US$23,321.55.

General Characteristics of Conference Abstracts

Of the 48 abstracts reviewed, there is a yearly publication frequency starting in 2003. The years in which the most publications were reported in 2011, 2013, 2015, and 2019. The distribution of articles published by country places Colombia in first place with 35.4%, followed by Brazil with 17%, Mexico with 10.4%, Costa Rica with 6.3%, Argentina, Chile, Ecuador, Guatemala and Venezuela each with 4.1%, and Honduras, Panama, Dominican Republic, El Salvador and collaboration between countries, each with 2.08%. In general, the time horizon of each abstract varies from 6 months to 50 years. From the analysis perspective, the supplier's perspective predominates at 66.6%. This perspective is broken down into the following categories: 37.5% from the point of view of the general supplier, 34.3% from the private supplier, 22% from the public supplier, and 6.2% from the mixed supplier. The following percentage of the analysis perspective, 33.3%, corresponds to that of the third-party payer. Regarding the method of information analysis, the results are distributed as follows: the most used is the decision tree (29%), followed by the Markov model and treatment simulations (18.7%). The predominant economic evaluation in the abstracts, in turn, is that of CE at 35%, followed by

cost analysis at 27%, Profitability study at 25%, CU at 9% and one study with a combination of CE and CU that accounts for 4%. A table and qualitative description of these summaries can be found in. ([Supplementary data 5](#)).

Discussion

This is one of the few studies that sought to synthesize and compile the most relevant information for evaluating the health costs of RA in Latin America. A novel strategy was developed to update the actual value of the costs to the current year. To determine the value in current prices of the costs of care and treatment of RA patients in the countries evaluated, the authors developed a financial methodology to update to present value the cost of the studies carried out in previous years. In this method, the exchange rate of the base year multiplied by the base price in dollars of the study was determined for each study, and the resulting value was weighted in accordance with the annual inflation index reported by the World Bank. The inflation result was adjusted to the country's currency and the exchange rate for the year 2023. Inflation thus estimated is considered indicative of the cost of living and reflects the loss of purchasing power of money, and the subsequent increase in the value of goods in the basic family basket of goods. In a way, it is a reflection of the savings possibilities for society and of the impact on the prices of essential drugs, such as those used for RA. This finding is similar to the one reported in the study done by Cid et al.[89] This report referred to the lack of financial protection that affects a large part of the population and also shows how there are groups of countries with greater difficulties than others due to the cost of medicine and exposure to greater situations of vulnerability and thus denotes great inequity. This same study, endorsed by the Pan American Health Organization (PAHO), identifies policies in some countries that could be associated with the evolution of financial protection. In addition, they concluded that public spending should be increased to increase the financing of health systems and transform them into a universal health model to replace out-of-pocket spending as shown in the study done by Petrera and Jiménez.[90]

From the review carried out, it is evident that the cost analyses are the most used (85%), and in a much higher proportion than other studies such as those of CE and CU. This is probably because these cost analyses are easier to implement based on financial records, equipment use, workforce and quality without involving the stage of measuring procedures and their results, which would cause more complexity in carrying out the CE. In the study by Catalá-López and García-Altés, carried out in Spain, they mention that the most predominant economic evaluation is that of CE at 62.5%.[91] This corresponds to the results of our review in which the predominant type of study in the abstracts was found to be CE but in a proportion of only 35%, and in the articles, it occupies the second place at 7.4%.

Moreover, several studies have shown that the direct cost of the disease increases depending on the phases, cycles, or years of treatment, particularly the cost associated with drugs with the cost of biological drugs being clearly higher. Likewise, in the ESPOIR cohort, which has included patients with early RA in France in a multicenter and consecutive manner, the study by Chevreul et al, showed that the direct cost was higher for users of biological therapies, especially for those who used them within the first year, followed by users who received them in consecutive years.[92] The authors conclude that their analysis suggests that early use of biologicals may reduce other health care costs by slowing disease progression although the extent to which the high direct costs of early use of biologicals may be offset by reduced need for surgeries or other procedures after the fourth year of disease is unknown. These statements as well as those in the above-mentioned study could be applied to the present review since, due to the type of design, the exact impact on cost reduction associated with this therapy is unknown. However, in some of the studies included, particularly in the Colombian population, it was shown that increasing the number of patients in remission and with low disease activity resulted in cost savings.

It should be noted that the present review did not focus on studies that analyze indirect costs or the burden of disease through DALYs. Other authors have recently reported, based on a systematic review of the literature, that these costs can represent up to 30% of the costs of the disease in the Latin American region.[8] In that review, the authors found a wide variability in these costs within the region that was similar to what was found in the present review with respect to direct costs or those with CE design since they varied from one country to another even when the same health technologies were analyzed. Thus, for example, the same group of anti-TNF drugs showed great variability in terms of costs in countries such as Brazil, Mexico, and Colombia.

It was not possible, however, to analyze studies that researched the economic impact of rotating or switching a patient between different anti-TNF drugs or switching to other therapies after using this class of drugs. Other reviews that have

addressed this issue have not included Latin American studies and, in fact, have highlighted the need for greater uniformity in the methodology used in economic evaluations of rotation versus switching strategies after the use of anti-TNF for patients with RA. It is not possible to draw conclusions about the costs attributed to dose escalation, particularly in drugs such as anti-TNF drugs.[93] Although there are previous reviews that have analyzed this issue, such as the one done by Moots RJ et al, in which only one article from the Latin American region was included, the authors concluded that, although there are different definitions and several methods were used to calculate dose escalation with biologicals, the results were consistent with the individual comparative studies.[94] In addition, not only are the costs of biological drugs increasing, but so are the total costs of RA.

A systematic review of the literature on the burden of disease in the biological era that was completed by February 2019, in turn, included a total of 72 articles from 28 countries of which only 3 were from Latin America, the same 3 included in the present review.[95] The other articles were dominated by the European continent. In that review, it was striking that the direct cost attributed to drugs has been increasing over the years from 2000 to 2016. The authors note that, due to different definitions in the limited number of studies, it was a challenge to compare the breakdown of costs. Just as in the present review, the heterogeneity and variability of these costs was large with drug costs contributing between 9.8% and 87.2% to direct costs.

With respect to the differentiation of costs by type of drug based on technology, it should be noted that the results of the present study did not include findings regarding biosimilars. However, the impact that these have on RA costs must be considered, a fact that is even more significant in Latin America given the economic restrictions of the health systems. Now, the introduction of biological therapy is known to have marked a substantial change in the course of RA. However, the costs of this therapy can cause difficulties in terms of access because the purchase prices are often high.[96] In view of the above, consideration should be given to the fact that large-scale production of these drugs could improve their introduction into the market and this fact will positively affect the accessibility of this medication in the future. It is well known that biosimilars have shown an efficacy and safety similar to the reference pharmaceutical products which translates into lower disease costs. From this perspective, greater access to biological therapies that can help to control more severe stages of the disease could be generated.[97,98]

In this regard, the study by Haustein R et al, estimated that between 2.3 and 11.7 billion euros could have been saved in Germany, France, and the United Kingdom between 2007 and 2020 with the introduction of biosimilars and concluded that these savings could have improved the quality of care and, above all, increased access to the various biological therapies.[99] Most of the cost analyses related to treatment with biosimilars have been with INF since it is the first product to have received approval for use in daily practice. Its profile has proven to be a CE therapy in disease control compared to the reference therapy although cost analyses have also been done with ETA biosimilar molecules and have shown some benefits.[100,101] This seems to demonstrate that the use of biosimilars in populations with diverse sociodemographic characteristics and different economic levels may have a certain advantage, and although many more studies are needed in Latin America to prove it, the introduction of biosimilars could change the tendency to use conventional therapy since greater access to biological therapy at a lower price would be sought. However, studies evaluating the cost-effectiveness of conventional vs biosimilar therapy are lacking.

In the last decade, the Pan American League of Rheumatology Associations (PANLAR) put forward a consensus statement on biosimilars that highlighted several points including proper pharmacovigilance and possible lower prices.[102] More recently, the study by González et al, analyzed the prices of biological drugs in the United States, Spain, and three Latin American countries.[103] The article highlights that the economic effort made by Latin American countries to get access to these drugs is much greater than that of the US and Spain.

The results show a difference between countries in the costs of care and treatment. This may be due to the acceleration of technological innovation and the increase in new drug molecules. This development is due to not only scientific but also economic reasons.[104] A report by the Chilean economic observatory states that the level of prices between countries is related to the higher level of productivity and income. The higher the productivity, the higher the prices tend to be. Tariffs, transportation costs in the international market, taxes and subsidies, labor costs, and the degree of competition in the market between generic and commercial drugs also play a role.[105] In the study done by Xu et al between 2000 and 2016, there was a decrease of 56% to 44% in out-of-pocket spending by families in almost all regions

of the world, mostly explained by the increase in public spending on health, the increase in co-payments, care fees, and drug costs that can reach 85% of out-of-pocket spending. This has resulted in a decrease in medical care, an increase in the number of patients who give up on treatment.[106]

Among some mitigation strategies include managing risk to identify the vulnerability of the population and applying treatments that reduce the progression of the disease and its complications. In the case of RA, the causal factors that can be effectively managed are early detection and suspicion of the disease while the factors that modify prognosis are manageable and contribute greatly to improving patient health outcomes.[107]

The preparation of updated recommendations, supported by scientific evidence, will provide guidance to rheumatology specialists and other professionals involved in the care of patients with RA. These recommendations will facilitate informed therapeutic decision making in order to mitigate the risks associated with treatment and improve patients' quality of life.[108]

However, the constant rise in health costs leads to the need to economically evaluate treatments in order to prioritize those that have and offer the best value or benefit related to the local context. The use of economic evaluations supports decision making in health care and represents a valuable mechanism for improving the efficiency of budget distribution among the different levels of health care, thus promoting the efficient use of resources.[109]

Limitations

Regarding the study limitations, the inclusion of conference abstracts, while broadening the scope of available evidence, may introduce potential limitations and bias related to the preliminary nature and quality of the data, which are discussed in the Supplementary Materials and acknowledged in this section. Also, a limitation of this study is the exclusion of studies from 2024, which may have resulted in missing recent publications, who can contribute further results. Additionally, the number of publications on economic evaluations of RA in Latin America is limited, and as such, we found more conference abstracts than full-text articles. This constraint is acknowledged and discussed in the Supplementary Materials, and it may affect the comprehensiveness of the findings. Additionally, Due to the heterogeneity of the included studies, we were unable to perform a meta-analysis of the costs or conduct a quantitative analysis. However, to maximize the use of the available data, we followed the SwiM guidelines for qualitative analysis, ensuring a thorough synthesis of the information extracted from the studies.

It had also not possible to determine how the cost of the disease affects the purchasing power and, therefore, the economic balance of both the population and the health system of each country, because there is no standardization of prices, as there is no single currency as in the European Union. On the other hand, the size of each economy, as indicated by the Gross Domestic Product (GDP) in Latin American countries, is very different compared with European countries, and inflation behaves differently, as do the indicators of wealth distribution, as reflected in World Bank reports.

Conclusion

The analysis of costs for Latin American patients with RA emphasizes the need for careful management of expenditures by insurers and care providers and highlights the relevance of sound health policies and risk management in the world's health systems. This study shows through cost analyses that the use of biological therapies makes up the majority of direct costs. In addition, there are important differences in the costs of biologics between different countries, as well as differences depending on the stage of disease progression. Therefore, it would be important that each country should implement strategies to make cost analyses from the payer perspective. Regional technology assessment agencies could play an important role in this regard. On the other hand, more research is needed in Latin American RA population with an emphasis on measuring health outcomes to strengthen cost analyses with the use of biosimilars versus traditional therapies.

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Disclosure

Adriana Rojas-Villarraga: reports Adriana Rojas-Villarraga reports fees for conferences from AbbVie, Amgen, Aztra Zeneca, Janssen, andPfizer in the last three years, and fees for conferences and grant for a research protocol fromAsoreuma (Colombian National Rheumatology Scientific Society) outside the submitted work and with no influence on it. Pedro Santos-Moreno reports fees for conferences from Abbvie, Abbott, Biopas-UCB, Bristol, Janssen, Pfizer, Roche, Sanofi, AbbVie, Abbott, Biopas-UCB, Bristol, Janssen, Pfizer, Roche, Sanofi. The authors report no other conflicts of interest in this work.

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