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Analysis of foot function in terms of different pharmacological treatments in a cohort of patients with rheumatoid arthritis: a longitudinal study

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Abstract

This study examines the influence of pharmacological treatments on foot functionality in patients with rheumatoid arthritis over a five-year period. A longitudinal analysis categorized patients into different treatment groups, assessing their foot function using the Foot Function Index (FFI) at the start and end of the study. The groups are based on their pharmacological treatment. Pharmacological treatment groups were categorized into: I methotrexate (MTX), II MTX plus biological treatments (including all variables), III biological treatment alone, and IV a miscellaneous group comprising patients with diverse treatments, including patients for whom various drugs had failed or who had not achieved remission with pharmacological treatment. The study included 206 RA patients with an average age of 58.32 years and a disease evolution of 15.28 years. The analysis of the FFI in total and across its domains of pain, disability, and activity revealed significant differences only in the pain domain ($p=0.011$), with a trend toward worsening over time observed in the other domains. Notably, MTX treatment showed improvement in the pain domain (decreasing from 45.76 in 2018 to 40.43 in 2023). Findings suggest that while pharmacological treatments are essential in managing rheumatoid arthritis, their impact on foot function is limited, with MTX demonstrating the most significant benefit in terms of pain reduction.

Keywords Pharmacological treatments, Foot function, Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammation and progressive joint deterioration, significantly affecting patients' quality of life. Its hallmark symptoms include joint pain and stiffness, leading to limitations in daily life activities [1, 2]. RA typically presents as symmetric polyarthritis with a gradual onset and progressive evolution, resulting in irreversible structural and functional deterioration [3], with anatomical deformity paralleling disease progression [2]. The disease predominantly affects the hands and feet. Not only this, but it also leads to a reduction in quality of life [4], functional ability [5] and self-care [6], as well as causing gait alterations [7].

Early RA frequently manifests with distinctive foot joint involvement and pain, which continue with the disease progression [8], leading to significant physical and psychosocial impairment [9]. Up to 90% of patients experience foot involvement, with the metatarsophalangeal and proximal interphalangeal joints being most commonly affected [10, 11], exhibiting deformities such as Hallux Abductus Valgus (HAV) and claw toes [12]. The midfoot, though less studied, is associated with advanced disease stages and decreased longitudinal arch height [10]. The hindfoot presents valgus deviation [13] and a high incidence of tibiofibular talus joint involvement are noted both at diagnosis and in long-term disease [11].

The use of disease-modifying rheumatic drugs (DMARDs) as part of treatment such as methotrexate (MTX), includes synthetic drugs aimed at controlling inflammation and also includes biological agents designed to halt the autoimmune response [14]. Initiating treatment in the early stages is crucial, with the therapeutic strategy focusing on tight control of inflammation and disease activity (treat to target). Treatment can be independent or combined, with first-line therapies recommended by international guidelines such as European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR). However, treatment should still be tailored to the clinical presentation of the patient and disease progression [15].

Treatment focused solely on inflammation is insufficient to prevent bone deterioration; however, targeted therapies (bDMARDs) aiming to inhibit key immune system components have shown clinical improvement and slowed bone erosion in patients [16]. It is essential to point out that not all patients exhibit significant clinical response, and these treatments do not provide a definitive solution for RA [17]. Adjuvant treatments include corticosteroids, with ongoing debate regarding their potential role in promoting [18] or preventing osteoporosis in RA patients [19]. In addition, non-pharmacological therapies are used, such as physiotherapy [20], physical exercise [21], psychological interventions [22], and foot orthoses [23], which are employed to address anatomical regions and clinical manifestations of RA.

To our knowledge, the impact of RA pharmacological treatments on foot function has not been evaluated. This novel article addresses this gap, offering new insights into the relationship between existing therapies and foot function, enhancing our understanding of the disease, and suggesting potential benefits for the functional ability of the patients. This study builds on previous research by shifting the focus from overall disease progression to the specific impact of pharmacological treatments on foot function in RA. While prior studies have examined joint deterioration and treatment efficacy, few have explored their long-term effects on foot mechanics. By addressing this gap, this research provides a more comprehensive perspective on RA management. The aim of our study was to explore foot function in patients with RA in terms of different pharmacological treatments received over a five-year period.

Methods

Patients and study design

This longitudinal study was conducted during two distinct data collection periods: from January 15 to June 15 in 2018, and from March 15 to July 15 in 2023. The research was centered at the Rheumatology Service of the University Hospital Virgen de las Nieves in Granada, Spain. In 2018, an observational cohort study included 246 patients diagnosed with RA following the 2010 classification criteria endorsed by the American College of Rheumatology and the European League Against Rheumatism. By 2023, 206 of these participants were re-evaluated.

In 2023, patients who declined to participate, had physical impairments that prevented walking, cognitive impairment, underwent foot or ankle surgery after June 2018 or died were excluded. Additional exclusions in 2018 covered people with comorbid musculoskeletal or neurological conditions and endocrine disorders such as diabetes mellitus. The Rheumatology Service team provided all eligible patients with detailed study information and obtained written informed consent prior to inclusion.

This study was conducted in compliance with the Declaration of Helsinki and authorization obtained by the ethical committees of the University of Malaga under the CEUMA-91 protocol (CEUMA-91-2015-H) and the Andalusian Health Service (PEIBA: ARC0001). The Rheumatology Service team provided all eligible patients with detailed study information and obtained written informed consent prior to inclusion.

Data collection

Demographic and clinical data, including age, gender, disease duration, and current therapy, were collected. The Spanish version of the Foot Function Index (FFI-Sp) [24], was employed to evaluate pain, functionality, and physical activity on a 0-100 scale, where lower scores denote better outcomes. Additionally, Visual Analogue Scales (VAS) for general and foot-specific pain [25] were utilized for correlation analyses.

Each study group consisted of patients who maintained treatment from 2018 to 2023, pharmacological treatments were classified into four categories: (I) methotrexate (MTX), (II) MTX combined with biological treatments (MTX + Bio), (III) biological treatments alone (Bio), and (IV) a miscellaneous pharmacological treatment that did not fit into any of the defined groups. In the case of Bio and MTX + Bio, changes of biological drug were accepted, (because it was not efficient or serious adverse effects), therefore, they remained in the same defined treatment group. Patients with MTX and MTX + Bio who had no modification in terms of their conventional DMARDs remained in the same group. If any patient underwent changes in their conventional DMARDs, they were moved to the group miscellaneous. A participant with MTX who had a combination with another conventional DMARDs has not been identified. Corticosteroid use, common across all groups during disease exacerbations, was not treated as an independent category. Changes in body mass index (BMI), Foot Posture Index (FPI), and Disease Activity Score (DAS-28) between 2018 and 2023 were also examined as potential confounding variables.

Procedure

Clinical assessments were conducted in a dedicated space by two independent researchers (A.R.C. and M.G.G.), who ensured standardized administration of the FFI-Sp which demonstrated high inter-rater reliability (ICC 0,85 to 0,97) and other tools. Participants' pharmacological treatments and health status changes over the study period were recorded to contextualize the clinical findings.

Statistical analysis

Descriptive statistics were applied to summarize the characteristics of the sample, with normality verification using the Kolmogorov-Smirnov test. ANCOVA was conducted to compare groups at different time points, controlling for baseline values.

Changes over time were analyzed using paired t-tests, while one-way ANOVA and Chi-square tests examined baseline group differences. A mixed-model ANOVA assessed treatment effects, incorporating post hoc Bonferroni corrections to minimize Type I errors. SPSS v.26 was used for all statistical analyses, with a significance threshold of $p < 0.05$.

Table 1 The distribution of patients by disease activity levels in 2018 and 2023

Activity level	2018 (%)	2023 (%)
Remission	68.93%	46.60%
Low	11.65%	17.48%
Moderate	16.50%	30.10%
High	2.91%	5.83%

Results

The study included 206 patients (75.43% women and 24.27% men) with a mean age of 58.32 years (SD = 12.43) and a mean disease duration of 15.28 years (SD = 10.38). The BMI was 27.21 (SD = 5.9) in 2018 and 26.68 (SD = 5.54) in 2023, with no statistically significant differences between time points ($p = 0.106$). The mean DAS28 score showed an overall increase from 2.15 in 2018 to 2.66 in 2023, suggesting a trend toward worsening disease activity over time (Tables 1 and 2).

When analysing these results by treatment group, a decrease in remission rates was observed across all groups, with a corresponding increase in moderate and high disease activity levels, particularly in Groups Bio and miscellaneous where moderate activity increased from 7.4% to 22.22% in 2018 to 45.45% and 43.18% in 2023, respectively (Table 3).

These findings indicate a decline in remission rates across all treatment groups, with an increase in moderate and high disease activity over time, particularly in biologic or combination therapy groups.

The analysis of the FFI from 2018 to 2023 revealed significant changes exclusively in the pain domain within the MTX group (from 45.76 in 2018 to 40.43 in 2023, $p = 0.011$). However, the disability and activity domains demonstrated a trend toward deterioration, albeit without statistical significance (Table 4).

Table 2 Description of groups, gender, age and pain

	Gender (women/men)	Age (2018)	VAS-general (2018)	VAS-foot (2018)	VAS-general (2023)	VAS-foot (2023)
MTX ($n = 42$)	80/20%	60.7 ± 13.03	4.6 ± 2.99	3.9 ± 3.07	5.62 ± 3.4	5.81 ± 3.1
Bio ($n = 115$)	85.71/14.29%	53.64 ± 11.11	5.71 ± 1.77	4.79 ± 2.46	5.18 ± 2.89	6 ± 2.4
MTX + Bio ($n = 33$)	67.65/32.35%	55.09 ± 12.37	4.53 ± 2.33	3.91 ± 2.75	5.59 ± 2.96	4.12 ± 2.49
Miscellaneous ($n = 16$)	77.78/22.22%	57.73 ± 8.85	5.8 ± 2.52	5.2 ± 3.03	6.43 ± 2.55	6.38 ± 2.50

VAS: Visual Analogue Scales; MTX: Methotrexate: Bio: Biological

Table 3 DAS28 scores and disease activity levels by treatment group in 2018 and 2023

Group	DAS28 2018	Remission 2018 (%)	Low 2018 (%)	Moderate 2018 (%)	High 2018 (%)	DAS28 2023	Remission 2023 (%)	Low 2023 (%)	Moderate 2023 (%)	High 2023 (%)
MTX ($n=42$)	1.72	90%	10%	0%	0%	2.46	50%	25%	18.75%	6.25%
Bio ($n=115$)	1.71	92.86%	0%	7.4%	0%	2.77	45.45%	9.09%	45.45%	0%
MTX + Bio ($n=33$)	2.1	73.53%	5.88%	17.65%	2.94%	2.1	75%	12.5%	12.5%	0%
Miscellaneous ($n=16$)	2.4	53.33%	20%	22.22%	4.44%	3.1	25%	20.45%	43.18%	11.36%

DAS: Disease Activity Score; MTX: Methotrexate: Bio: Biological

Table 4 Comparison of foot function index scores by treatment group in 2018 and 2023

FFI score	MTX ($n=42$)	Bio ($n=115$)	MTX + Bio ($n=33$)	Miscellaneous ($n=16$)	*p*-value
Total FFI (2018)	42.16 (24.1)	41.68 (28)	37.58 (24.9)	38.59 (22.2)	0.077
Total FFI (2023)	41.1 (22.7)	47.13 (26.1)	43.97 (23.3)	52.96 (20.3)	
FFI Pain (2018)	45.76 (22.9)	41.48 (26.7)	40.09 (25.07)	39.19 (21.7)	0.011
FFI Pain (2023)	40.43 (20.8)	47.20 (26.7)	48.55 (20.1)	50.81 (19.9)	
FFI Disability (2018)	42.79 (27.4)	43 (30.2)	37.67 (27.4)	42 (26.1)	0.301
FFI Disability (2023)	37 (25.8)	42.43 (27.2)	38.15 (27.9)	51.06 (21.8)	
FFI Activity (2018)	8.43 (9.9)	11.9 (13.7)	8.67 (9.4)	7.56 (8.9)	0.077
FFI Activity (2023)	11.12 (11.8)	12.43 (10.9)	10.3 (9.8)	16.63 (12.4)	

FFI: Foot Function Index; MTX: Methotrexate; Bio: Biological

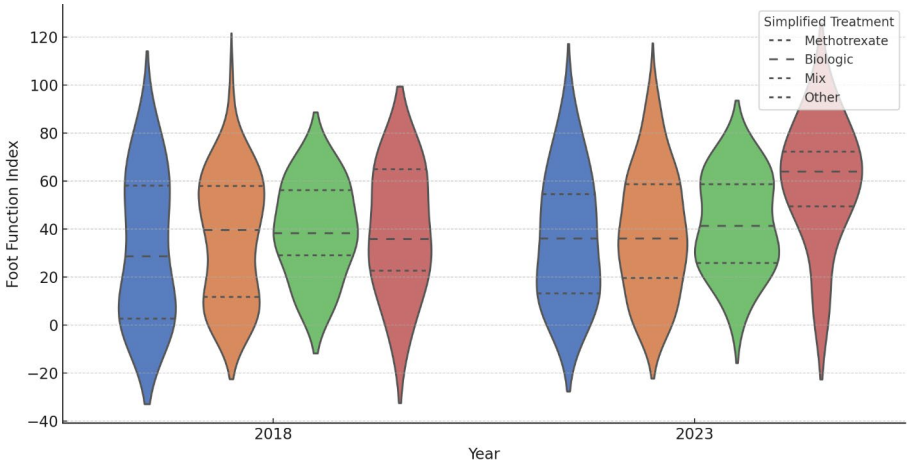

Fig. 1 Comparative analysis violin plot of foot function index and domains changes by pharmacological treatment categories in rheumatoid arthritis patients, 2018 vs. 2023

These findings suggest that MTX monotherapy was associated with a statistically significant reduction in pain, whereas biologic and combination therapies demonstrated a trend toward worsening in this domain. No significant differences were found in disability or activity domains.

Figure 1 represents the distribution of the FFI in 2018 and 2023 across four different treatment groups: MTX, Bio, a combination of both MTX + Bio, and a miscellaneous group. The violin plots illustrate the variability and distribution of FFI values within each treatment group, while individual dots represent the values of individual patients. The black dots within each violin plot indicate the mean FFI for each treatment group, with error bars representing ± 1 SD. In 2018, the distribution of FFI was more variable across all treatment groups, whereas in 2023, a more homogeneous pattern emerged. The MTX + Bio group showed a noticeable reduction in FFI variance, suggesting a potential stabilization in foot function over time. The Bio and MTX groups exhibited relatively consistent FFI scores between both time points, while the miscellaneous group showed a broader distribution in 2023.

These findings suggest that treatment type may influence foot function over time, with combined therapies potentially leading to greater stabilization. Further statistical analysis is required to determine the significance of these trends.

Discussion

The primary objective of this study was to investigate foot function in patients with RA based on the administered treatments over a five-year period.

The FFI scores and its sub-levels observed in the present study cohort align with those reported by Inoue E. et al., reporting an increase in FFI associated with age and disease activity level [26]. Schneider W. et al. (2016) found that both the total FFI and its subscales for pain and disability showed a non-uniform increase with age, marginally higher in females, in a healthy population [27]. Compared to these studies, the findings presented in this study did not show significant changes related to age, disease activity, or gender.

Current RA treatment protocols inadequately assess foot joints because standard disease activity measures, like DAS-28, exclude them, despite their high involvement in RA. Clinical assessments and imaging primarily focus on larger joints, overlooking foot-related pain, deformities, and mobility issues. Additionally, the lack of foot-specific outcome measures and historical underrepresentation in research contribute to incomplete evaluations, limiting the effectiveness of treatment strategies. Integrating foot assessments into RA management is essential for a more comprehensive understanding of disease impact and patient care.

The presented results indicated that pharmacological treatments do not improve or maintain foot function, showing higher overall FFI scores and sub-levels. MTX was the only treatment exhibiting a non-statistically significant decrease in its values compared to the rest of the treatments, which saw increases across all levels.

Combined treatments (MTX + Bio) demonstrated lower values than monotherapy treatments in both 2018 and 2023, except in the FFI pain sub-level, where they showed similar values. The increase from 2018 to 2023 in this group was greater than in the monotherapy groups.

Combined pharmacological treatments are posited to facilitate more rapid and effective achievement of disease remission, enhancing the overall treatment efficacy. However, achieving remission, as denoted by a score of DAS28 on the designated scale, does not singularly dictate the progression or mitigation of foot function loss [28]. This is a crucial consideration, as foot function significantly impacts patient mobility and quality of life. Notably, current methods for assessing disease activity often overlook the involvement of foot joints. This oversight introduces a significant bias in our understanding and evaluation of treatment outcomes. The exclusion of foot joints from activity assessments could obscure the full impact of the disease on patient mobility and underrepresent the benefits of treatments that might specifically improve foot function. Consequently, there is a pressing need for the integration of comprehensive foot joint evaluations into disease activity assessment protocols to ensure a holistic understanding of treatment efficacy and patient well-being. This approach would enable a more nuanced assessment of therapeutic outcomes, highlighting the importance of targeting both disease remission and the preservation of foot function to optimize patient care strategies.

Patients categorized within the miscellaneous group, which encapsulates those subjected to a variety of treatments owing to unsuccessful drug therapies or challenges in identifying a pharmacological approach that effectively induces remission, consistently reported the highest FFI values. The experiences of this group are particularly telling, illustrating not just a numerical increase in FFI scores but a significant escalation in functional impairment over a span of five years. This trend underscores the profound impact of treatment failures on patient well-being, both physically and psychologically.

This leads to a substantial decline in their quality of life. Chronic pain and physical limitations not only hinder daily activities but also lead to higher levels of fatigue, depression, and anxiety, further diminishing overall well-being [29]. Additionally, unrelieved foot-related disability exacerbates gait abnormalities, increasing the risk of falls and further restricting physical activity, which contributes to social isolation and reduced participation in work and leisure activities [30]. These factors highlight the urgent need for personalized treatment approaches that address both the physical and emotional challenges faced by RA patients with persistent disease activity.

The difficulties encountered in this patient subset highlight the complexities of managing RA, where a one-size-fits-all treatment strategy is often inadequate. A comprehensive study by Conigliaro et al. explores the multifaceted repercussions of failed pharmacological treatments on patients with RA, providing insightful data on the escalation of FFI scores in relation to treatment efficacy and patient-reported outcomes. This work corroborates the critical need for personalized treatment plans that go beyond achieving remission to address the comprehensive functional and emotional needs of patients [31].

Longitudinal studies examining RA treatment in relation to osteoarticular deterioration progression, such as the study by Levitsky A. et al. (2015), found that patients responding to combined treatments (MTX + Bio) had less radiographic progression than monotherapy patients at two and five years, suggesting long-term benefits of combined therapy [32]. Unlike monotherapies, combined treatments (MTX + Bio) initiated at disease diagnosis lead to remission and halt joint damage more quickly. However, these treatments presented an impact in the short-term joint deterioration without necessarily affecting pain and function levels.

The results from the present study differ, showing that long-term foot function deterioration in the combined treatment group (MTX + Bio) equals that of disability and physical activity levels in monotherapy treatments and is significantly worse compared to MTX alone [28, 33].

Osteoarticular damage in RA contributes to deformity, directly linked to increased pain and foot function deterioration [34, 35]. Otter SJ. et al. concluded that foot pain in RA patients is associated with disease duration, stiffness, and numbness, with treatment and age not significantly related [30].

High pain levels are predictive of long-term disability in RA patients [29, 36]. In the longitudinal study by Andersson M. et al. from the early 2000s, disability levels were directly related to activity level, pain, radiological progression, and aging, not to the assigned treatment, noting that the era marked the beginning of biologic treatments with differing therapies and recommendations [37].

Activity limitation results support recent systematic reviews, finding that functional incapacity, stiffness, and age are determinants of physical activity in RA patients [38, 39].

To our knowledge, this is the first study to examine the impact of pharmacological treatment on foot function in RA patients over five years. Overall results tend to increase but are not statistically significant.

Strengths

This is a novel study correlating treatment with foot function over a substantial five-yearperiod with a large sample size and the need for personalized, multidisciplinary approaches in treating patients with failed pharmacological interventions, emphasizing improved foot function and mobility as crucial outcomes beyond achieving remission.

Limitations

Standardized evaluation methods for activity control do not include foot joints, potentially overlooking a critical aspect of RA management and patient quality of life.

Conclusions

This study provides relevant evidence on the relationship between pharmacological treatments and foot function in RA patients over time. The present study shows that while pharmacological interventions, particularly combined treatments (MTX + Bio), are pivotal in managing RA, their impact on foot function does not mirror the clinical remission often observed. MTX alone showed a slight improvement in foot function, though the change was not statistically significant. This contrasts with the rest of the treatments, which either led to a decline or showed no improvement in foot function. The miscellaneous treatment group, characterized by heterogeneous treatments due to previous treatment failures, exhibited the most considerable deterioration in foot function over the study period. This research highlights the necessity for incorporating foot-specific evaluations into standard RA treatment and assessment protocols to fully understand and address the multifaceted impacts of RA on mobility and quality of life of the patients.

Future studies should explore long-term treatment effects on RA-related foot function, integrating advanced imaging, patient-reported outcomes, and multidisciplinary interventions to improve mobility and quality of life.

Abbreviations

RA	Rheumatoid arthritis
DMARDs	Disease modifying antirheumatic drugs
MTX	Methotrexate
HAV	Hallux abductus valgus
bDMARDs	Biologic disease-modifying antirheumatic drugs
FFI	Foot function index
FFI-Sp	Spanish version of the foot function index
VAS	Visual analogue scale
BMI	Body mass index
FPI	Foot posture index
DAS-28	Disease activity score

Supplementary Information

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Supplementary Material 1

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Author contributions

All authors made substantial contributions to the conception and design of the work; MGG and ARC the acquisition and analysis of the data; ABOA and GGN interpretation of data; LRP have drafted the work and ELR and MPR substantively revised it. All authors have approved the submitted version.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in compliance with the Declaration of Helsinki and authorization obtained by the ethical committees of the University of Malaga under the CEUMA-91 protocol (CEUMA-91-2015-H) and the Andalusian Health Service (PEIBA: ARC0001). Written informed consent prior to inclusion was obtained from all eligible patients.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare no competing interests.

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