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ORIGINAL ARTICLES

Real-world safety data of first-line drugs for rheumatoid arthritis: insights from the Portuguese Reuma.pt database

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ABSTRACT

Objectives: To assess adverse events (AE) associated with first-line therapies for rheumatoid arthritis (RA) in a real-world setting.

Material and Methods: Retrospective multicenter cohort study of patients fulfilling classification criteria for RA and followed up in 66 rheumatology centers from the Rheumatic Diseases Portuguese Registry (Reuma.pt). All AE reports associated with first-line disease-modifying antirheumatic drugs (DMARDs) up to November 2024 were included. Demographic and clinical data were analyzed, and AE characteristics were investigated. Categorical and continuous variables were compared using chi-square tests and Mann–Whitney U tests, respectively. Statistical significance was defined as $p < 0.05$.

Results: Among 1 880 AE entries, 377 (20.1%) were attributed to first-line DMARDs, most commonly methotrexate (62.9%) although no information on drug dosage was available. The median age at AE occurrence was 58.6 years (IQR: 19.32), and 82% were female. A causality assessment was available in 317 reports, with 40.3% deemed "probable," 28.1% "possible," and 10.6% "definitive." Severe AE were reported in 13.2% of cases, with pulmonary involvement being the most common (20.8%). Overall, 46.7% of patients discontinued treatment for any reason. Male sex was significantly associated with severe AE (OR = 2.31; 95% CI: 1.17–4.55; $p = .014$), and older patients were more likely to experience severe AE (median age 65.7 vs. 57.9 years; $p < .001$). The most affected body organ systems were gastrointestinal (9.3%), skin (8.2%), and hematological (8.2%). The median time to AE onset from treatment initiation was 1.27 years (IQR: 2.63), and from disease onset was 8.56 years (IQR: 11.76).

Conclusions: AE related to first-line RA therapies can lead to significant clinical consequences, including treatment discontinuation. Male sex and advanced age were associated with increased AE severity. The most affected systems appear consistent with known drug safety profiles, particularly that of methotrexate; however, the absence of information regarding drug dosage precludes more detailed conclusions. These findings emphasize the need for individualized monitoring strategies and improved pharmacovigilance to optimize long-term treatment safety and adherence in RA management.

Keywords: Rheumatoid Arthritis; Antirheumatic Agents; Methotrexate; Adverse Drug Reaction Reporting Systems; Treatment Outcome.

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KEY MESSAGES

- Older patients experience more severe adverse events; many discontinue treatment even when events are non-severe and causality is unclear.
- Early diagnosis and prompt DMARD treatment are crucial; many adverse events occur soon after treatment despite long disease duration.
- Most adverse events linked to first-line DMARDs affect women, but men have twice the risk of severe adverse events.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder that primarily affects the synovial joints, leading to inflammation, pain, stiffness, and progressive joint destruction[1–4]. Early diagnosis and a combination of pharmacologic and non-pharmacologic therapies are key to managing this chronic and debilitating disease effectively[2,5,6].

Disease-modifying antirheumatic drugs (DMARDs) are key therapeutic agents for RA, aiming to reduce synovitis, systemic inflammation, and improve function[7]. Methotrexate (MTX) is the leading conventional DMARD (cDMARD) and can be combined with other cDMARDs, namely Leflunomide and Sulphasalazine. Biological DMARDs (bDMARDs), including tumor necrosis factor inhibitors (TNFi), are employed when treatment goals are not achieved with first-line therapies or when adverse events (AEs) associated with conventional DMARDs (cDMARDs) necessitate discontinuation[7].

The use of cDMARDs and bDMARDs for RA treatment has been associated with various AE[8–13 14]. High burden of AE has been associated with higher disease activity and lower likelihood of remission in early RA[15]. Additionally, lack of knowledge on how to manage adverse events has been identified as a key contributor to poor adherence to DMARD therapy, as shown in the OBSERVAR study[16].

While glucocorticoids (GCs) are effective in managing early arthritis, their long-term use is associated with a broad spectrum of adverse effects, including weight gain, osteoporosis, osteonecrosis, hyperglycemia, cardiovascular events, increased susceptibility to infections, gastrointestinal complications, psychiatric disturbances, and suppression of the hypothalamic–pituitary–adrenal axis[17]. MTXis generally well-tolerated but can be related with significant side effects leading to treatment discontinuation. These include liver toxicity, cytopenias, gastrointestinal symptoms and alopecia[14,18,19]. Liver toxicity is a notable concern, especially in patients with pre-existing liver conditions such as fatty liver disease.

bDMARDs, including TNFi (e.g. infliximab, etanercept, adalimumab), have shown significant efficacy but come with serious AE such as infections and administration site reactions[9,13]. Respiratory infections, including pneumonia and, most notably, tuberculosis in association with anti-TNF agents, represent among the most serious adverse events associated with bDMARDs. Risk factors include older age, concomitant

corticosteroid use, underlying respiratory conditions[20], chronic renal failure, previous splenectomy, and hypogammaglobulinemia[21]. Baricitinib is a JAK inhibitor, a targeted synthetic DMARD (tsDMARD), and has shown efficacy in treating RA but is associated with safety concerns, particularly thromboembolism, which limits its use to patients who have failed other treatments[22].

Long-term observational studies and registry data are crucial for understanding the safety profiles of these agents. Although randomized controlled trials (RCTs) have identified differences in the efficacy and safety of these therapies, their findings are inherently constrained by strict inclusion and exclusion criteria, limited follow-up durations, and highly controlled treatment settings. As a result, RCTs may not capture the full range of adverse events or reflect the variability in patient characteristics encountered in everyday clinical practice, such as advanced age, multimorbidity, or concomitant medication use. Therefore, there is a critical need to complement RCT evidence with real-world data, which offers a more representative and ecologically valid assessment of treatment safety across broader and more diverse patient populations. No real-world evidence on the safety of first-line DMARDs in patients with RA was identified in the Portuguese population, underscoring the need for locally relevant data to support informed treatment decisions. This highlights the need for the present study, which leverages real-world data that more accurately reflect routine clinical practice, offering a more comprehensive and applicable understanding of treatment safety across diverse patient populations.

In Portugal, the Reuma.pt registry provides a valuable source of real-world data on RA patients. However, comprehensive analyses comparing the safety of first-line therapies using data from this registry remain limited.

The primary objective of this study is to evaluate and characterize AE associated with first-line rheumatoid arthritis therapies in a real-world Portuguese cohort, utilizing data from the Reuma.pt registry. A secondary objective is to explore demographic predictors of AE, aiming to enhance risk stratification and inform personalized treatment strategies.

METHODS

Study Design and Setting

We conducted a multicenter retrospective cohort study including all patients with RA, identified based on the 2010 ACR/EULAR classification criteria and/or clinical diagnosis as documented by the attending rheumatologist, up to November 2024, focusing on AE associated with first-line therapeutic agents. The analysis addressed AE associated with first-line therapeutic agents, defined as those occurring under the drug registered as the patient's initial treatment in the Reuma.pt registry.

Study Population and Data Collection

We collected data on age, sex, first-line drugs and their causal relationship with the AE ("probable", "possible", "definitive", "unlikely"), AE severity ("serious", "non-serious"), treatment discontinuation ("yes" or "no"), outcomes after treatment discontinuation ("recovery", "in recovery", "recovery with sequelae", "persists" without recovery", "death possibly related to the AE", "unknown"), drug reintroduction ("yes" or "no"), previous AE ("yes" or "no"), treatment and disease duration until the occurrence of an AE, and the organs and systems involved in the AE. Causal relationship between the drug and the AE, as well as AE severity, are parameters recorded in Reuma.pt and are determined based on clinical judgment.

Data Source: Reuma.pt Registry

These clinical data were registered in Reuma.pt, established in 2008 by the Portuguese Society of Rheumatology. It is a prospective, observational, web-based registry that collects longitudinal real-world clinical data from patients with rheumatic diseases across multiple rheumatology centers in Portugal. RA is one of the diseases included in Reuma.pt, for which the registry gathers detailed information on diagnosis, disease activity, treatment strategies, comorbidities, laboratory and imaging results, and patient-reported outcomes. Data are entered by trained rheumatologists as part of routine clinical practice, at variable time points (ideally at each patient visit), with no mandatory fields enforced in the data collection process. This flexibility, while supporting clinical workflows, may result in incomplete datasets and variability in data quality.

Reuma.pt is not an inception cohort, as patient inclusion in the registry may occur several years after disease diagnosis and treatment initiation. Additionally, retrospective data referring to clinical events prior to the establishment of the registry may be entered, depending on the availability of historical medical records. Consequently, the timing of data collection in relation to disease onset or therapeutic milestones may vary across patients, which may introduce challenges in establishing temporal relationships or comparing treatment trajectories.

Ethical Considerations

This study was approved by the Reuma.pt Coordination and Scientific Boards. Reuma.pt was approved by

National Data Protection Board and by the local Ethics Committees. Written informed consent is obtained from all patients at the time of their inclusion in the Reuma.pt registry. The study protocol was approved by the Ethics Committee of the Unidade Local de Saúde da Cova da Beira (approval number 64/2023), in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

All analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 29. Continuous variables were summarized using medians and interquartile ranges (IQRs), given the non-normal distribution verified through the Kolmogorov–Smirnov test. Comparisons between sexes for continuous variables—disease duration and time from treatment initiation to AE onset — as well as differences in age according to AE severity were assessed using the non-parametric Mann–Whitney U test. Categorical variables were presented as absolute and relative frequencies, and differences between sexes in the severity of the AE and clinical outcome were assessed using the chi-square (χ^2) test. Missing data were not subject to imputation and were handled through a complete-case approach for each analysis. Specifically, analyses involving categorical variables and percentage calculations were performed using only available (valid) cases, excluding missing observations from denominators. The extent of missing data was assessed descriptively to evaluate its potential impact on study findings. Statistical significance was set at $p < .05$.

RESULTS

A total of 1 880 AE, corresponding to 1 029 patients, were recorded in Reuma.pt at the time of data extraction. Among these, 377 AE (20.1%) were attributed to first-line DMARDs used in the treatment of RA, with MTX accounting for 237 cases (62.9%) (Table I). Most AE related to first-line DMARDs occurred in female patients (309 cases; 82.0%). The median age at the time of the adverse event was 58.6 years (interquartile range [IQR]: 19.32). The median time from drug initiation to AE onset was 1.27 years (IQR: 2.63), while the median disease duration at AE onset was 8.56 years (IQR: 11.76). The distribution of time from drug initiation to adverse event occurrence for each drug is presented in Table II. RA had been ongoing for over 40 years in 193 reports (51.1%) at the time of data collection.

Causality assessment was possible for 317 reports. Of these, the relationship between the drug and the AE was classified as "probable" in 152 cases (40.3%), "possible" in 106 (28.1%), "definitive" in 40 (10.6%), and "unlikely" in 19 (5.0%). Forty-eight AE (13.2%) were classified as severe. Treatment discontinuation occurred in 176 cases (46.7%), of which 136 (81.4%) were classified as non-severe and 31 (18.6%) severe. Considering the cases where treatment was discontinued, the causal relationship between the adverse event and the drug was assessed as probable in 88 (52.4%), definitive in 30 (17.9%), possible in 45 (26.8%) and unlikely in 5 cases (3.0%).

No potential drug–drug interactions were identified in 227 reports (77.5%). Regarding clinical outcomes, recovery following the AE was documented in 227 of all reported cases (70.5%). In 83 cases (48.0%), no prior similar reaction had been reported. Drug reintroduction was attempted in 64 cases (31.5%).

Among first-line treatment-associated AE (n = 364), 48 (13.2%) were severe and 316 (86.8%) were non-severe. In severe cases, the respiratory (n = 10; 20.8%) and hematologic systems (n = 7; 14.6%) were most frequently affected. Less common were the gastrointestinal (n = 3; 6.3%), nervous (n = 3; 6.3%), and musculoskeletal systems (n = 1; 2.1%). In non-severe cases (n = 316), the gastrointestinal system was most commonly affected (n = 32; 10.1%), followed by the hepatobiliary system (n = 29; 9.2%), the skin and appendages (n = 27; 8.5%), and hematologic system (n = 24; 7.6%). No significant sex-based difference was observed in treatment duration until AE onset ($U = 2{,}463.5$, $Z = 0.308$, $p = .758$). In contrast, disease duration prior to AE onset differed significantly between sexes, with females presenting a longer median disease duration (9.84 years; IQR = 12.38) compared to males (6.16 years; IQR = 9.66) ($U = 10{,}141$, $Z = 2.62$, $p = 0.009$).

A statistically significant association was found between sex and AE severity ($\chi^2(1)$, $N = 364 = 6.07$, $p = 0.014$). Severe AE were reported more frequently in male (22.4%) than females (11.1%). The odds of experiencing a severe AE were significantly higher in male compared to female (OR = 2.31, 95% CI: 1.17 – 4.55).

Age was also associated with AE severity: participants with severe AE were older (median 65.67 years, IQR = 12.76) than those with non-severe events (median 57.92 years, IQR = 18.87), as indicated by a Mann-Whitney U test ($U = 10413.50$, $Z = 4.17$, $p < 0.001$).

DISCUSSION

This study analyzed the occurrence of AE associated with first-line DMARDs in patients with RA, based on 377 reports collected up to November 2024. MTX was the most frequently implicated DMARD, accounting for 237 cases. This predominance likely reflects its role as

TABLE I. Descriptive summary of adverse event episodes: demographics, suspected drugs, affected organs, severity, causality, treatment, and outcomes (N = 377)

Variable	n (%)	Female (n = 309)	Male (n = 68)
AE severity			
Non-Severe	316 (86.8)	264 (88.9)	52 (77.6)
Severe	48 (13.2)	33 (11.1)	15 (22.4)
Missing	13	-	-
First-line Drug			
Methotrexate	237 (62.9)	184 (59.5)	53 (77.9)
Etanercept	41 (10.9)	39 (12.6)	2 (2.9)
Infliximab	27 (7.2)	25 (8.1)	2 (2.9)
Sodium aurothiomalate	18 (4.8)	13 (4.2)	5 (7.4)
Sulfasalazine	13 (3.4)	11 (3.6)	2 (2.9)
Tocilizumab	12 (3.2)	12 (3.9)	0 (0.0)
Hydroxychloroquine	11 (2.9)	9 (2.9)	2 (2.9)
Adalimumab	10 (2.7)	10 (3.2)	0 (0.0)
Leflunomide	2 (0.5)	2 (0.6)	0 (0.0)
Abatacept	1 (0.3)	0 (0.0)	1 (1.5)
Azathioprine	1 (0.3)	1 (0.3)	0 (0.0)
Baricitinb	1 (0.3)	0 (0.0)	1 (1.5)
Tofacitinib	1 (0.3)	1 (0.3)	0 (0.0)
Organ system			
Gastrointestinal system	35 (9.3)	27 (8.7)	8 (11.8)
Skin	31 (8.2)	29 (9.4)	2 (2.9)
Hematological system	31 (8.2)	22 (7.1)	9 (13.2)
Hepatobiliary system	29 (7.7)	23 (7.4)	6 (8.8)
Respiratory system	21 (5.6)	15 (4.9)	6 (8.8)
Nervous system	4 (1.1)	3 (1.0)	1 (1.5)
Ophthalmological system	3 (0.8)	2 (0.6)	1 (1.5)
Reproductive system	2 (0.5)	2 (0.6)	0 (0.0)
Urinary system	1 (0.3)	2 (0.6)	0 (0.0)
Ear	1 (0.3)	1 (0.3)	0 (0.0)
Musculoskeletal system	1 (0.3)	1 (0.3)	0 (0.0)
Other	2 (0.5)	1 (0.3)	1 (1.5)
Causal relationship			
Probable	152 (40.3)	123 (39.8)	29 (42.6)
Possible	106 (28.1)	89 (28.8)	17 (25.0)
Definitive	40 (10.6)	33 (10.7)	7 (10.3)
Unlikely	19 (5.0)	15 (4.9)	4 (5.9)
Treatment discontinuation			
No	201 (53.3)	167 (54.0)	34 (50.0)
Yes	176 (46.7)	142 (45.9)	34 (50.0)
Drug interaction			
No	227 (77.5)	195 (78.9)	32 (69.6)
Yes	66 (22.5)	52 (21.1)	14 (30.4)
Missing	84	-	-

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TABLE I. continuation

Variable	n (%)	Female (n = 309)	Male (n = 68)
Clinical outcome			
Recovery	227 (70.5)	188 (60.8)	39 (57.4)
In recovery	36 (11.2)	32 (10.4)	4 (5.9)
Recovery with sequelae	15 (4.7)	13 (4.2)	2 (2.9)
Persists without recovery	13 (4.0)	11 (3.6)	2 (2.9)
Death possibly related to the AE	5 (1.6)	4 (1.3)	1 (1.5)
Unknown	26 (8.1)	21 (6.8)	5 (7.4)
Missing	55	-	-
Prior similar reaction			
No	83 (48.0)	122 (71.3)	26 (74.3)
Yes	30 (17.3)	28 (16.4)	4 (11.4)
Unknown	60 (34.7)	21 (12.3)	5 (14.3)
Missing	204	-	-
Drug rechallenge			
No	109 (53.7)	93 (54.4)	16 (50.0)
Yes	64 (31.5)	54 (31.6)	10 (31.3)
Unknown	30 (14.8)	24 (14.0)	6 (18.8)
Missing	174	-	-

AE – adverse event.

TABLE II. Minimum, maximum, median, and interquartile range (IQR) of the time in years from drug initiation to adverse event occurrence, by drug

Drug	Minimum	Maximum	Median	IQR
Etanercept	0.0	17.07	1.83	3.01
Golimumab	0.08	1.09	0.59	-
Infliximab	0.35	12.17	2.60	4.1
Methotrexate	0.02	19.12	1.34	2.48
Sulfasalazine	0.41	0.73	0.423	0.25
Tocilizumab	0.23	2.83	0.52	0.77
Adalimumab	0.0	2.54	0.99	1.18

the cornerstone of RA management, and its widespread use as initial therapy. A greater proportion of AE occurred in female patients, although male patients were significantly more likely to experience severe events. In addition, older age was associated with increased AE severity. Nearly half of the patients discontinued treatment following an AE, despite over 80% of reported cases being classified as non-severe. The gastrointestinal tract, skin, and hematologic systems were the most commonly affected organs, consistent with the known safety profile of conventional DMARDs. An additional and notable finding was the discrepancy between disease duration and treatment duration at AE onset. Many AE occurred relatively soon after treatment initiation, while several patients had long-standing disease, suggesting substantial delays in initiating therapy. This likely reflects historical treatment practices, particularly in patients diagnosed decades ago, when DMARD initiation was often delayed after prolonged symptomatic management. The inclusion of patients diagnosed over 40 years ago supports this hypothesis. Nevertheless, reporting bias must be considered due to the retrospective design and potential inaccuracies in recording disease and treatment timelines. Interestingly, most treatment discontinuations were due to non-severe AE (81.4%), and a definitive causal relationship with the suspected drug was confirmed in only approximately 18% of these cases. This raises concerns regarding the

decision-making process surrounding therapy suspension, suggesting that treatments may be prematurely discontinued when causality is uncertain and the AE does not pose a major safety threat. While patient discomfort and risk perception undoubtedly influence adherence, these results emphasize the importance of robust causality assessment and enhanced patient education to appropriately balance the risks and benefits of continuing therapy. Strengthening shared decision-making and improving communication between clinicians and patients could help prevent unnecessary discontinuations and maintain disease control.

The predominance of MTX-related AE is consistent with its established role as first-line DMARD recommended by national and international guidelines[23]. The higher number of AEs observed in women reflects the greater proportion of female patients in the study cohort, consistent with the known higher prevalence of RA in females and does not imply an increased risk of AE associated with female sex. However, a higher frequency of AE in women is supported by previous studies identifying female sex as a risk factor for adverse drug reactions[24,25] and related hospital admissions[26]. Conversely, the increased severity of AE in males is also documented, potentially reflecting biological and behavioral differences such as immune regulation, hormone levels, pharmacokinetics, comorbidities, and healthcare-seeking behavior[27]. The earlier occurrence of AE in men may indicate a lower threshold for developing toxicity or a faster progression to clinically significant reactions. Behavioral factors, differential exposure to comorbidities, or patterns of healthcare utilization may also contribute[28]. These sex-related differences in the severity of adverse drug reactions are not unique to RA, as similar patterns have also been observed in other rheumatic diseases, such as psoriatic arthritis[29]. The association between older age and more severe outcomes is similarly supported by the literature[30–32], which often highlights age-related physiological vulnerability and reduced adaptive capacity as risk factors for poor drug tolerance and recovery. Data from the BIOBADASER and RABBIT registries, both of which prospectively monitor the safety of bDMARDs and tsDMARDs in patients with RA, consistently show that older age and female sex are associated with a higher risk of AE. In BIOBADASER, patients aged 65–74 and ≥75 years had a 42% and 89% increased risk of AEs, respectively, compared to younger adults, while female patients also showed a significantly higher incidence[31]. Similarly, RABBIT data indicated that serious adverse events, particularly infections and cardiovascular or neurological complications, occurred more frequently in older individuals and in women[33]. Nonetheless, some studies have reported inconsistent findings regarding age and AE severity, suggesting that other confounding variables, such as polypharmacy or baseline health status, may play a significant role[34,35].

The distribution of affected organ systems observed in this study aligns with the established safety profiles of commonly used first-line therapies for RA, particularly MTX and other conventional DMARDs, which are frequently associated with gastrointestinal toxicity, dermatologic manifestations, and hematological abnormalities[18,20]. These findings are consistent with previous research that have reported similar patterns of organ system involvement in patients undergoing treatment for RA[36].

The proportion of therapy discontinuation in the present study is in line with rates reported in previous studies[37,38], suggesting that AE remain a significant barrier to sustained treatment in routine clinical practice. In the context of RA, treatment discontinuation carries important drawbacks, including the potential for disease flare-ups, progression of joint damage, and reduced long-term functional outcomes[15]. Guidelines such as those from EULAR and ACR offer valuable frameworks for monitoring and managing AE in RA treatment[39,40]; however, clinical judgment and individualized care are essential to tailor decisions to each patient beyond standardized recommendations.

Taken together, these results reinforce the importance of patient-specific risk stratification when initiating DMARD therapy, with particular attention to age, sex, and other individual characteristics that may modulate susceptibility to AE. The finding that a high proportion of patients discontinued treatment due to AE, even when these were non-severe and not definitively linked to the drug, underscores the critical need for early detection, proactive management, accurate causality assessment, and shared decision-making in order to optimize adherence and prevent unnecessary treatment interruptions.

The strengths of this study include the relatively large sample size and the focus on real-world data, which offers insights into the safety of DMARDs as they are used in routine clinical practice. However, several limitations should be considered. The retrospective design is inherently prone to underreporting and missing data, which likely led to an underestimation of the true incidence and spectrum of AE. The absence of information on drug dosage at the time of the event precluded analysis of dose-dependent effects. In addition, the lack of data on patient comorbidities and concomitant medications limited the ability to adjust for confounding factors. The relatively small number of male patients further restricted the power to draw definitive conclusions about sex-based differences.

Future research should address these limitations by

adopting prospective designs with standardized, comprehensive data, collection including detailed drug exposure, dosage, treatment duration, comorbidities, and concomitant therapies. Prioritizing sex- and age-specific analyses will help elucidate biological and clinical mechanisms underlying differential AR risk. Investigating historical treatment practices and their long-term impacts may yield valuable insights, particularly in cohorts with longstanding disease. Finally, development and implementation of standardized causality assessment tools and patient education strategies may support informed treatment decisions and improve long-term outcomes in RA.

CONCLUSIONS

This multicenter, real-world study provides a comprehensive overview of AE associated with first-line therapies for RA, with MTX identified as the most frequently implicated agent. Although most reported AE were non-severe, nearly half of the cases led to treatment discontinuation, highlighting the significant clinical impact of these reactions. Male sex and older age were significantly associated with increased AE severity, underscoring the need for tailored risk stratification and vigilant monitoring in these patient subgroups. The gastrointestinal, dermatologic, and hematologic systems were the most commonly affected, consistent with the established safety profiles of conventional DMARDs, especially MTX. Despite limitations related to missing data and potential underreporting, these findings emphasize the importance of ongoing pharmacovigilance in routine clinical practice. They also support the development of targeted strategies aimed at minimizing AE-related treatment interruptions. Future research should incorporate detailed clinical, pharmacological, and comorbidity data to better characterize individualized safety profiles and ultimately improve long-term treatment outcomes in patients with RA.

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