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ORIGINAL RESEARCH

From Conventional to Advanced Therapies: A National Health Registry Report (2016-2022) on DMARDs in Rheumatoid Arthritis Treatment in Turkey

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Objective: There are national and international guidelines on the optimal use of disease-modifying anti-rheumatic drugs. In this study, we aimed to provide critical insights into the real-world efficacy and adherence of these DMARDs, providing a data-driven basis for optimizing treatment paradigms for RA within the national healthcare framework.

Methods: This nationwide cohort study utilized data from the Turkish Ministry of Health National Electronic Database, known as E-Pulse between January 2016 and December 2022. In this analysis, cases of RA were identified using ICD-10 codes two times at least 30 days apart Treatment prescriptions were recorded based on their prescription at baseline and follow-up.

Results: There were a total of 347,902 RA (79.5% female) patients in the E-Pulse system. The mean (SD) age of RA patients was 59.1 (14.8) years Methotrexate and sulfasalazine (35.1% vs 30.5%, OR 95% CI 0.81 usage was more common in men and hydroxychloroquine was more common in women 46.764 (13.4%) patients were prescribed bDMARD and/or tsDMARD 494.499 times. AntiTNF drugs are the most commonly prescribed drugs. This is followed by B-cell blockers, JAK inhibitors, anti-IL6 and T-cell blockers.

Conclusion: Turkish national health database highlights the widespread use of synthetic DMARDs in treating rheumatoid arthritis (RA). While traditional DMARDs like methotrexate and hydroxychloroquine are favored the cautious use of advanced therapies, particularly anti-TNFs, suggests a potential for optimizing treatment protocols.

Keywords: rheumatoid arthritis, treatment, nation-wide, disease modifying drug

Key Points

1. Etanercept and β-blocker treatments have the longest duration of use based on real-life data.
2. Biosimilar usage rates vary between 10.8 and 27.7% among their drug groups.
3. Real-life data is considered to select the most effective and long-acting treatment regimens for patient.

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Introduction

Rheumatoid arthritis (RA) is a chronic, erosive, disabling inflammatory rheumatic disease. Because of the burden it places on patients, it should be treated with disease-modifying drugs (DMARDs) unless otherwise indicated. DMARDs are divided into three different subgroups as conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). csDMARDs are used as first-line after diagnosis. Commonly used agents include methotrexate, leflunomide, sulfasalazine and hydroxychloroquine. If these treatments are ineffective and/or intolerable, more advanced treatment options as b/tsDMARDs can be used as either combination or monotherapy. These agents include anti-TNF, B-cell blockers, T-cell blockers, anti-IL6 and Jak inhibitors.[1,2]

There are national and international guidelines on the optimal use of DMARDs. The most used guidelines are the EULAR and ACR recommendations.[1,2] CsDMARDs, such as methotrexate, leflunomide, and sulfasalazine, primarily modulate immune responses to slow disease progression. In contrast, bDMARDs target specific inflammatory pathways, such as TNF or IL-6 inhibition, to achieve a more selective immune response. Targeted synthetic tsDMARDs, including JAK inhibitors, act by blocking intracellular signaling pathways to control inflammation.[3] On the other hand, treatment options are determined according to the conditions of each country. In Turkey, while csDMARDs are recommended in the first phase, advanced therapies can be used without sequencing in case of ineffectiveness or intolerance. People living in Turkey are covered by general health insurance. Therefore, full, and uninterrupted access to treatment is available for those who qualify, regardless of the cost of advanced therapies. It was highlighted that RA patients in Turkey impose a significant economic burden, with higher disease activity necessitating the use of biologic therapies.[4] Additionally, Malhan et al reported that the cost of care for RA and ankylosing spondylitis patients in Turkey increases substantially with advanced therapies. Among biologic therapies, biosimilars can also be used, especially in anti-TNF and B-cell blockers.[1,2]

In this study, we embarked on a detailed comparative analysis, using the extensive data from a nationwide electronic health registry system, to dissect and examine the patterns of use and persistence of synthetic versus advanced DMARD therapies in the treatment of rheumatoid arthritis (RA). By delving into the nuances of therapeutic distribution and persistence rates, this research aims to provide critical insights into the real-world efficacy and adherence of these disease-modifying agents, providing a data-driven basis for optimising treatment paradigms for RA within the national healthcare framework.

Methods

Turkish Ministry of Health National Electronic Data Base

This nationwide cohort study utilized data from the Turkish Ministry of Health National Electronic Database, known as E-Pulse. Since 2014, the Ministry of Health has implemented comprehensive health data warehouses that span the entire country. In 2015, the Ministry established the "e-Pulse" system as a national health information system, accessible only to authorized individuals and institutions. This system, boasting extensive bandwidth, encompasses the entirety of the country.[5] Turkey operates under a universal system named General Health Insurance (GHI), granting all residents access to medical services without charge through the Social Security Institution (SSI). All study data were sourced from the central national database mentioned earlier, overseen by the Turkish Ministry of Health.

The Ministry of Health employs Big Data technology to deliver services, with integrated systems such as e-Pulse and the National Healthcare Information System (NHIS). The E-Pulse system contains clinical records for more than eighty million individuals in Turkey, encompassing demographic details, laboratory results, drug history, and comorbidities. This study was conducted according to the Declaration of Helsinki and the Ministry of Health Ethical Board approved the study (95741342–020/27,112,019).

Patient Selection

Patients with RA were selected as follows: Patients with RA ICD-10 codes [M05 ("M05.0", "M05.1", "M05.2", "M05.3", "M05.8", "M05.9"), M06 ("M06", "M06.0", "M06.2", "M06.3", "M06.4", "M06.8", "M06.9")] two times at least 30 days apart AND with at least one DMARD prescription AND without spondyloarthritis and/or psoriatic arthritis ICD codes were included.

Treatments of Rheumatoid Artritis

Data recorded in the e. Pulse system between January 2016 and December 2022 were used. csDMARDs (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine) and glucocorticoids (prednisolone, methylprednisolone, deflazacort) were recorded according to use at any time. From 2019, the use of csDMARDs and glucocorticoids in newly diagnosed RA patients were also recorded.

The use of bDMARDs and tsDMARDs was recorded according to their prescription at baseline and follow-up. tsDMARDs (tofacitinib, baricitinib) and bDMARDs, anti-TNF (adalimumab, infliximab, golimumab, certolizumab, etanercept), anti-IL-6 (tocilizumab), T-cell blocker (abatacept), B-cell blocker (rituximab) were recorded. Biosimilar bDMARDs were recorded as adalimumab (amgevita), infliximab (remsima, ixifi), rituximab (rituximab, truxima, reditux). The hospitals where the advanced therapies were prescribed and the prescription pattern by physician (rheumatology and/or physical therapy physician) were also recorded.

Statistical Analysis

Data were analyzed using SPSS Statistics for Windows, Version 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Numerical variables were presented as absolute numbers, percentages, and means with standard deviations. The Kolmogorov–Smirnov test was used to determine data distribution. The Student's *t*-test was employed for comparing continuous data, for categorical variables, the chi-square test was used for comparison. A p-value of less than 0.05 was considered statistically significant.

The time to change of the first advanced therapy was calculated and expressed as a Kaplan-Meier curve. In this calculation, the time to 50% of the population used the medication used was also calculated. Estimated days were also calculated for each drug. Estimated days are the number of days until the number of people using a drug decreased to 50%. Analyses were performed on both a drug and a group basis. To take into account the pandemic period, the years before the pandemic were also calculated separately for 2018 and 2019 as 2016 and 2017 also included accumulated patient load from previous years.

Results

General Characteristics of RA Patients

There were a total of 347,902 RA patients in the E-Pulse system, of whom 276.544 (79.5%) were women. The mean (SD) age of RA patients was 59.1 (14.8) years (59.5 (15.6) in men and 59.1 (14.6) in women). Rheumatoid factor was positive in 207,437 (59.9%) patients (52.9% in men and 61.7% in women).

Use of Synthetic DMARDs and Glucocorticoids in RA Patients

Patients' use of csDMARDs and glucocorticoids is shown in Table 1. Methotrexate and sulfasalazine use was more common in men and hydroxychloroquine use was more common in women (Table 1).

Initial b/tsDMARDs Prescription in RA Patients

The rates of initial drug prescription according to advanced treatment subtypes in the follow-up hospitals are shown in Table 2. Anti-TNF drugs are the most commonly prescribed drugs. This is followed by B-cell blockers, JAK inhibitors, anti-IL6 and T-cell blockers. Advanced treatments in RA patients were prescribed by the following branches: Rheumatology 66.9%, Physical Therapy and Rehabilitation (PT) 18.3%, Pediatric Rheumatology 2.4%, Gastroenterology 0.9%, Dermatology 0.7%. PT doctors preferred anti-TNFs more frequently than rheumatology doctors (61.8% vs 46.9%, $p<0.001$).

Total Use of b/tsDMARDs in RA Patients

Between 2016–2022, 46.764 (13.4%) patients were prescribed bDMARD and/or tsDMARD 494.499 times. The number of these prescriptions according to treatment groups is shown in Figure 1. The usage list according to the active substance is also shown in Supplementary Figure 1. Distribution of bDMARDs according to provinces is given in Supplementary

Table 1 Distribution of Ever-prescribed cs DMARDs and Glucocorticoids by Gender

Medications	All RA Patients n=347.902	Female RA Patients n=276.544	Male RA Patients n=71.358	OR (95% CI)
Methotrexate	194.716 (55.9)	152.217 (55.0)	42.499 (59.6)	0,83 (0,81–0,84)
Leflunomide	116.412 (33.5)	93.257 (33.7)	23.155 (32.4)	1,06 (1,04–1,08)
Sulfasalazine	109.472 (31.5)	84.434 (30.5)	25.038 (35.1)	0,81 (0,79–0,83)
Hydroxychloroquine	217.678 (62.6)	181.204 (65.5)	36.474 (51.1)	1,82 (1,79–1,85)
Glucocorticoids	282.590 (81.2)	223.493 (81.1)	59.097 (82.8)	0,89 (0,87–0,91)
Prednisolone	184.651 (53.1)	145.932 (52.8)	38.719 (54.3)	0,94 (0,93–0,96)
Methylprednisolone	178.239 (51.2)	141,543 (51.2)	36.696 (51.7)	0,98 (0,96–0,99)
Deflazacort	24.667 (7.1)	20,106 (7.3)	4561 (6.4)	1,15 (1,11–1,19)

Table 2 The Rates of Drug Prescription According to Advanced Treatment by Specialties and Center Type

	Anti-TNF	B-cell Blocker	JAK Inhibitor	Anti-IL-6	T cell Blocker
Overall prescription in dependent of department/hospital categories (%)	49.4	23.3	14.4	8.6	4.2
Rheumatology (%)	46.9	24.7	14.3	9.8	4.2
Physical Therapy and Rehabilitation (%)	61.8	9.9	15.2	6.3	6.9
University Hospital (%)	47.9	27.7	10.3	8.5	5.6
Secondary/Tertiary care hospitals (%)	52.3	18.5	16.9	8.7	3.6
Private Hospitals (%)	49.2	22.7	16.4	10.2	1.5
Private and Foundation Universities (%)	41.6	41.8	10.5	4.3	1.8

Figure 2. Route of b/ts DMARDs were subcutaneous 263.819 (53.3%), intravenous 183.514 (37.1%), and oral 47.166 (9.5%). Tocilizumab and abatacept had both iv and s.c options. Tocilizumab i.v and abatacept i.v form were 73.1% and 62.4%, respectively. The use of anti-TNF biosimilars among all bDMARDs is 5.3% and the use of biosimilars among

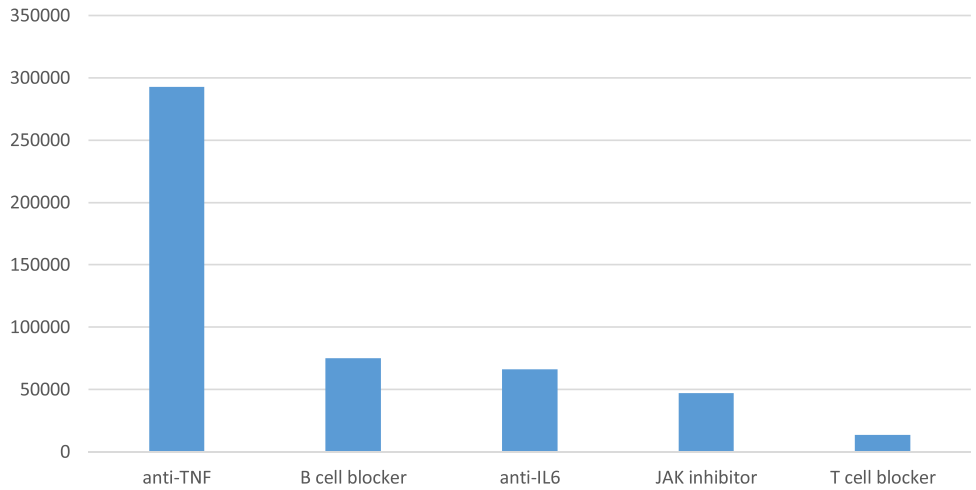

Figure 1 The number of b/tsDMARD prescriptions according to treatment groups.

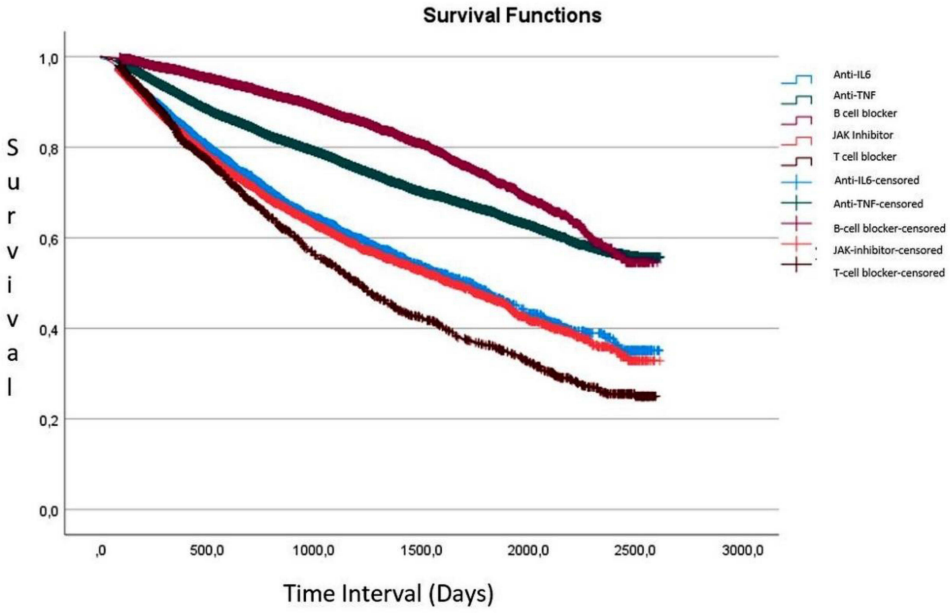

Figure 2 Drug survival by month on a drug group basis.

anti-TNFs is 10.8%. The use of B-cell blocker biosimilars among all bDMARDs is 4.2%, and the use of B-cell blocker biosimilars is 27.7%.

Continuation of b/Ts DMARDs in RA Patients

The continuity of the first advanced treatment according to the drug groups is shown in Figure 2 and distribution of bDMARDs according to provinces were added as a supplementry Figüre 2. According to this, the best drug group-based continuity was observed for B-cell blockers. This is followed by anti-TNFs. Anti-IL6 and Jak inhibitors showed a similar rate of drug retention, while the lowest drug retention was observed with T cell blockers. The time to first change of all drugs is shown in Supplementary Figures 3A and B. Supplementary Figures 3A (2700 days) and B (720 days) show drug switching rates by month on a drug-by-drug basis.

The time until half of the patients on b/tsDMARD continued the drug was calculated in days (Table 3). Accordingly, the best-estimate days were 2125 for etanercept (95% CI 2010–2239 days) and 2111 for B cell blockers (95% CI 2085–2138 days).

Table 3 Time to Drug Discontinuation in 50% of RA Patients Receiving Advanced Therapy

Group	Drug name	Estimate	SE	95% Lower	95% Upper
Anti-TNF	Adalimumab	1204	46	1113	1294
	Etanercept	2125	58	2010	2239
	Infliximab	1722	101	1523	1920
	Golimumab	1569	86	1399	1738
	Certolizumab	1494	60	1376	1613
B-cell blocker		2111	13	2085	2138
Anti-IL6		1734	66	1603	1864
JAK inhibitor	Tofacitinib	1539	46	1448	1631
	Baricitinib	582	7	568	597
T cell blocker		1204	46	1113	1294

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Discussion

This study evaluated the treatment choices of RA patients enrolled in the Turkish national health registry system between 2016 and 2022. Patients using at least one cs and/or b/tsDMARD were analysed. About 13% of all RA patients were found to be on advanced treatment. csDMARDs, mainly methotrexate and hydroxychloroquine, sulfasalazine and leflunomide, were used as an important treatment option. At least 80% of patients had used glucocorticoids at some point in their lives.

In Turkey, the E-Pulse system started to be used effectively after 2016. Therefore, in our study, we reported the distribution of treatments used between 2016 and 2022. In other words, when the distribution of DMARD use is given, it should be noted that the distribution of DMARDs used by the patients during their entire follow-up is not given because it does not go back to earlier then 2016. In fact, it should be stressed that this time limitation is the reason why methotrexate, which was the most preferred drug in our patients, remained at 56% in the whole group of patients. In other words, a certain group of patients may have used methotrexate and stopped before 2016. Glucocorticoids, which are commonly used in the treatment of RA, were also found to be used by around 80% of patients. According to data from a similar electronic registry system in France for 2010–2019, the rate of glucocorticoid use with any systemic treatment was calculated at 78% and methotrexate use at 49%, which is similar to our data.[6] In RABBIT, the German national registry of biological and synthetic DMARDs, 62.5% of 3851 RA patients using only conventional DMARDs used methotrexate.[7] Our patients also frequently used other csDMARDs, especially hydroxychloroquine, leflunomide and sulfasalazine.

When all advanced therapies are taken into account, anti-TNF drugs account for about half of all prescriptions. This is followed by B cell blockers, Jak inhibitors, anti-IL6 and T cell blockers. Selection rates for advanced treatment vary between countries. For example, in the United Kingdom, of approximately 33,000 RA patients on advanced therapy (other than JAK inhibitors) registered in the BSRBA-RA, 16% used B-cell blockers, 8% anti-IL6 and 3.5% T-cell blockers, while more than 70% used anti-TNFs.[8] In the German RABBIT registry, 57% of the approximately 10,000 patients receiving advanced therapy used anti-TNF, 14% B-cell blockers, 12% anti-IL6, 8% T-cell blockers and 7% Jak inhibitors.[7] In the Swedish ARTIS registry, 60% of the approximately 32,000 patients receiving advanced therapy were on anti-TNF, 13% on B-cell blockers, 11% on T-cell blockers, 8% on anti-IL6 and Jak inhibitors.[9] Although the distribution of advanced therapies varies according to country economic conditions and reimbursement policies, anti-TNF therapies appear to be the most preferred advanced treatment option.

B-cell blockers were found to have the longest duration of drug retention in our study, while T-cell blockers had the shortest persistence among bDMARDs. Real-world data from European RA registries support this observation, indicating that B-cell depletion therapies like rituximab may have sustained efficacy, particularly in seropositive RA patients.[10] T-cell blockers may have shorter persistence rates because of their more selective mechanism of action, which can lead to variable responses among patients. Further research that examines patient-specific factors, such as serology status, disease duration, and previous treatment history, is necessary to improve drug selection strategies.[11]

In Turkey, there is no significant cost difference between originator and biosimilar therapies. Clinicians can choose either the originator molecule or biosimilars as an anti-TNF, there is no cascading. Clinicians chose biosimilar anti-TNFs in only about 10% of anti-TNF cases. For B-cell blocker therapies, some centers require inpatient use, so biosimilar B-cell blockers are used in about 30% of B-cell blocker treatments. These results show that a significant proportion of physicians continue to use the originator molecule when it is up to the physician and when there is no difference in cost.

13% of all RA patients use at least one ts/bDMARD. Ts/b DMARDS usage ratio are variable in different European countries, overall ratio was almost 19%.[12] The rate of b-tsDMARD use in the French electronic health registry is 22%.[6] In the field of rheumatology, observational registries allow us to access important clinical/treatment data due to the large number of patients. However, for specialised patient groups such as RA, registries generally record patients admitted to hospitals in tertiary centers.[13] A significant proportion of RA registries only include biologic and targeted synthetic DMARDs, patients on synthetic DMARDs are used as a control group and not all patients are included. Therefore, it is not possible to see the distribution of all RA patients from these registries. The French electronic registry system and our E-Pulse system are unique in that they cover more than 90% of the country. The E-Pulse database regularly records every

medicine prescribed, as reimbursement is based on this record. As a result, there are no missing data for patients receiving advanced treatment. Therefore, it provides very valuable data in terms of reflecting the country in general.

Several factors, such as national health care policies, physician preferences, and accessibility of biosimilar therapies, could contribute to the observed differences in DMARD prescription patterns in Turkey compared to other countries.[14] Previous studies have highlighted that physician familiarity, cost-effectiveness concerns, and regional prescription trends significantly influence drug selection.[15] The increasing use of b/t DMARDs in RA treatment has important implications for both patient outcomes and healthcare costs. Although advanced therapies can improve disease control and potentially improve long-term functional outcomes, their higher costs require careful selection to ensure cost-effectiveness. Reducing financial burdens while maintaining treatment efficacy can be achieved through the availability and use of biosimilars. Treatment persistence is crucial for maximizing both clinical benefits and resource utilization. Future research should examine the balance between therapeutic effectiveness and economic sustainability in managing RA.

There are no data on the efficacy and safety of modern DMARDs in the E-Pulse system. Therefore, it is not correct to comment on the efficacy/safety of any DMARD. However, we do have longitudinal information on drug persistence, as the dates of patients' advanced treatment prescriptions are known. The reason for a patient to discontinue may be ineffectiveness or discontinuation of the drug due to side effects, patient-doctor request or disease control. Therefore, all these conditions should be taken into account when commenting on national data. Factors predicting continuation of advanced DMARD treatment were analysed as a subanalysis. However, as the activity and functional status of the patients was not known, the factors found (such as age, gender) were not presented in the manuscript, as they would not be very healthy. According to the E. Pulse data, drug retention is highest with B cell blockers as the first preferred advanced therapy, followed by anti-TNFs. T cell blockers have the lowest drug retention. When interpreting these results, it should be borne in mind that anti-TNF drugs are available in 5 different types and can be switched within themselves. When analysing the advanced therapies themselves, it should be taken into account that etanercept and B-cell blockers have the longest drug duration, with 50% of patients remaining on the drug for around 6 years, while the shortest duration was calculated for adalimumab and abatacept at around 3 years. Abatacept is available in Turkey, but has not been actively promoted since 2018. The short duration of drug persistence may be related to this lack of active promotion. This situation is important with regard to the specific conditions in each country.

The potential of personalized medicine driven by biomarkers to optimize treatment strategies is highlighted by the evolving landscape of DMARD therapy in RA. Personalized therapeutic approaches can be influenced by specific biomarkers, such as genetic polymorphisms and cytokine profiles, as suggested by emerging evidence.[16] Regulatory agencies have approved biologic therapies targeting IL-1, IL-6, and TNF pathways, revolutionizing treatment paradigms for juvenile idiopathic arthritis (JIA), and similar advancements have shaped the management of JIA.[17] By improving drug selection and minimizing adverse effects, we can enhance patient outcomes by expanding our understanding of these precision medicine approaches. New insights into optimizing the use of DMARDs for various inflammatory rheumatic diseases may be gained through future research that integrates real-world data with biomarker-driven algorithms. A more refined, patient-centered approach in rheumatology may ultimately result from these advancements, reinforcing the importance of continuous re-evaluation of treatment guidelines in accordance with emerging scientific evidence.

This study, while comprehensive in its analysis of DMARD utilization patterns across a nationwide cohort, is not without its limitations. The retrospective design, relying on registry data, may introduce certain biases related to coding accuracy and completeness of the records. Additionally, the E-Pulse system captures data post-2016, which may not fully reflect the historical medication usage patterns of patients diagnosed prior to this year. It is also worth noting that registry-based studies do not capture the entirety of clinical decision-making nuances, such as the rationale behind treatment selection, changes, and discontinuations. Moreover, the lack of detailed clinical outcomes data, such as disease activity, inflammatory marker levels and RA-related complications within the E-Pulse system precludes the ability to directly correlate DMARD use with efficacy and safety outcomes. Such limitations underscore the need for a cautious interpretation of the results, warranting further prospective studies to validate our findings.

In conclusion, our findings from the Turkish national health database provide a valuable snapshot of the current landscape of RA treatment options, underscoring the predominance of synthetic DMARDs in clinical practice. A data-driven approach that considers both clinical efficacy and cost-effectiveness is necessary to optimize advanced therapies, according to the observed trends. The utilization patterns observed reflect a cautious approach towards advanced DMARDs, with a notable reliance on conventional therapies such as methotrexate and hydroxychloroquine. Other healthcare systems may find these insights valuable, particularly when trying to balance access to innovative treatments with sustainable resource allocation. This study lays the groundwork for future research aimed at enhancing the understanding of DMARD treatment dynamics and encourages a strategic re-evaluation of treatment guidelines to better align with emerging evidence and clinical practice needs.

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Disclosure

The authors report no conflicts of interest in this work.

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