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Age-Specific Patterns in Biologic and Targeted Synthetic DMARDs Discontinuation and Drug-Specific Risks

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ABSTRACT

This study aims to analyse and delineate the predictor factors linked to the likelihood of treatment failure, encompassing adverse drug reactions (ADRs) or inefficacy. The specific focus of this investigation is on elderly Malaysian rheumatoid arthritis (RA) patients undergoing therapy with biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs). An observational, prospective longitudinal study on individuals with RA used Cox proportional hazards regression to compare treatment failure risk due to ADRs or lack of effectiveness across age groups. To ensure contributing factors related to treatment failure, adjustments were made for factors such as age, gender, disease duration, comorbidities, smoking, DAS28, and steroid use. In a cohort of 270 patients, 32.2% were classified as elderly. The elderly group exhibited higher RA disease activity, measured by DAS28 ESR, compared to the younger population (mean DAS28 ESR 6.748 versus 5.916, $p<0.001$). Regarding treatment, elderly individuals were more likely to receive biologic and targeted synthetic DMARDs as monotherapy rather than combination therapy (52.9% versus 47.1%, $p = 486$), with non-TNF inhibitors being more prevalent than TNF inhibitors (50.6% versus 37.9%, $p = 0.040$). Notably, the administration of targeted synthetic DMARDs in the elderly showed a significant negative association with treatment failure compared to TNF inhibitor therapy (adjusted HR: 0.12, 95% CI: 0.038, 1.265, $p<0.001$) after adjustment. Noteworthy predictors of failure in both biologic and targeted synthetic DMARD therapies, encompassing comorbidities, polypharmacy, smoking, corticosteroid use, and gender, were discerned. The utilisation of targeted synthetic DMARDs among elderly RA patients suggests a potentially more suitable and secure treatment option compared to biologic DMARDs. The identified predictors hold potential significance for guiding clinical decisions, particularly in the context of considering the discontinuation of biologic and targeted synthetic DMARDs in patients.

Keywords: Rheumatoid arthritis, biologic DMARD, targeted synthetic DMARD, treatment failure

INTRODUCTION

Biologic and targeted synthetic disease modifying anti-rheumatic drugs (DMARDs) are commonly administered to patients who have experienced treatment failure with methotrexate and/or other conventional DMARDs (csDMARDs). Previous research revealed that biologic DMARDs are recommended when the treatment objective is not attained using csDMARDs and in the presence of unfavorable prognostic factors. The prompt

initiation of biologic DMARDs has demonstrated efficacy in slowing down the advancement of clinically significant radiographic progression (Silvagni et al., 2018). The participation of individuals aged 65 years and above in clinical trials for RA is limited, resulting in data primarily derived from post hoc analyses. Although observational studies have investigated the effectiveness and safety of biologic and targeted synthetic DMARDs in patients aged 65 years old and above, the findings are inconsistent (Filippini et al., 2010; Genevay et al., 2007; Hetland et al., 2010; Hyrich et al., 2006; Ishchenko & Lories, 2016; Krams et al., 2016; Ochi et al., 2021; Radovits et al., 2009; Yun et al., 2015; ZENG et al., 2023). Several studies have reported a decrease in the effectiveness of TNF inhibitors (Hetland et al., 2010; Radovits et al., 2009), while some other studies revealed high efficacy of biologic and targeted DMARDs (Yun et al., 2015; Zeng et al., 2023) in elderly patients. However, other studies have not found any correlation between age and treatment response (Filippini et al., 2010; Hyrich et al., 2006; Ochi et al., 2021) or rates of drug discontinuation (Genevay et al., 2007; Ochi et al., 2021). The rationales for discontinuation of biologic and targeted synthetic DMARDs may vary based on age, with older individuals discontinuing more frequently due to adverse events, while younger individuals discontinue due to inefficacy (Busquets et al., 2011; Filippini et al., 2010; Ochi et al., 2021). Additionally, antibody diversity decreases with age, resulting in a decline in the ability to produce specific antibodies. It is plausible that the synthesis of ADA, which counteracts the impact of TNF inhibitors, may be comparatively less vigorous in the geriatric population, thereby diminishing the likelihood of subsequent inefficacy and obviating the necessity for concurrent immunosuppressive therapy (Jourdain et al., 2024). Several characteristics, particularly the presence of comorbidities, have been identified as factors that elevate the adjusted relative risk in patients with other chronic diseases (Kristin et al., 2023). Extensive efforts have been undertaken to ascertain individuals with RA who are more susceptible to treatment failure which is explained by discontinuation of therapy due to inefficacy or adverse drug reactions and necessitating change of therapy. Nonetheless, the existing literature has significant gaps, particularly regarding the influence of age. Although the effectiveness and safety of biologic DMARDs has been investigated in the elderly population, the findings are inconclusive.

This study aimed to determine the factors associated with the probability of treatment failure in elderly patients with RA due to ADR or lack of efficacy. The investigation overview assesses the influence of several variables, such as age, gender, duration of illness, comorbidities, adherence to medication, and treatment plan, on the likelihood of treatment failure.

MATERIALS AND METHODS

Patients' population

The present study considered all individuals diagnosed with RA who were initiating treatment with biologic or targeted synthetic DMARDs as eligible for inclusion in the analysis. As per the classification by the Public Service Delivery and Local Government of Malaysia, individuals who have attained the age of 60 years and above are considered as elderly or senior citizens. Therefore, the study population were split into two groups, < 60 and ≥ 60 years, based on the ages at which biologic and targeted synthetic DMARDs were administered.

Baseline data

Baseline data was gathered, encompassing information on demographic characteristics, comorbidities, smoking status, duration of RA, assessment of RA disease activity using the Disease Activity Score-28 (DAS28-ESR), classification of DMARDs, concurrent utilization of csDMARDs, and exposure to corticosteroids. The comorbidities were extracted from the medical records of the patients, utilizing a predetermined inventory of concurrent ailments. The assessment of comorbidity burden was conducted through the utilization of the Rheumatic Disease Comorbidity Index (RDCI), which is comprised of 11 comorbid conditions that are weighted based on their past or present occurrence. The RDCI demonstrates a commendable performance in accurately forecasting outcomes that are specific to RA, encompassing disability, medical expenses, hospitalization, and mortality (England et al., 2015). Information pertaining to adverse events was extracted from the medical records of the patients. Data were collected at regular intervals of 3 months throughout the initial 12-month period.

Statistical analysis

The baseline characteristics were evaluated to determine statistically significant disproportionality using appropriate statistical tests such as Chi-square, Mann-Whitney, or t-tests. The Cox proportional hazards regression was employed to conduct a comparative analysis of the risk associated with discontinuation of biologic and targeted synthetic DMARDs across different age groups due to any cause, including adverse drug reactions (ADRs) and lack of efficacy. To address potential confounding factors, a multivariable adjustment was conducted for a range of baseline covariates, such as age, gender, duration of disease, Rheumatic Disease Comorbidity Index, smoking status, Disease Activity Score 28 (DAS28), and utilization of steroids.

Ethical approval

The Malaysian Research Ethics Committee and National Medical Research Registry approved this study under the protocol number NMRR 20-2919-53875.

RESULTS AND DISCUSSION

Patient characteristics

Of 270 patients, 148 patients had no previous exposure to biologic or targeted synthetic DMARDs therapy and were starting their first therapy with these agents. The study population consisted of individuals, of whom 67.5% were below the age of 60. The average age of the entire populat

ion was 54.10 years, with a standard deviation of 10.218. Furthermore, the mean duration of the disease among the participants was 10.45 years, with a standard deviation of 5.391. Additionally, the baseline mean DAS28 ESR was recorded as 5.826, with a standard deviation of 1.130.

There were noteworthy differences observed between age groups (<60 and ≥60) in terms of the burden of comorbidities, disease activity, and prescribed medications. Patients aged > 60 years old demonstrated a higher burden of comorbidity in contrast to the younger population (78.2% had an RDCI score ≥ 1, as compared to 73.2%, p = 0.049). This was accompanied by a higher frequency of hypertension, osteoarthritis, respiratory diseases (asthma, COPD, and lung fibrosis), diabetes mellitus, and osteoporosis. respiratory disorders, including asthma and lung fibrosis, hypertension, and peptic ulcer disease, highlight the significance of considering the overall health status when making treatment decisions. In a prior study addressing a distinct chronic disease, specifically Type 2 diabetes and mental illness, comparable findings emerged, demonstrating that 59.2% and 65% of the patient population presented with comorbid conditions concurrent with their primary illness as well as polypharmacy (Ariyanti et al., 2022; Meraya et al., 2020).

On the other hand, the disease activity of RA quantified through the measurement of DAS28 ESR, exhibited a higher level within the group of individuals ≥ 60 and above (mean DAS28 ESR 6.748 compared to 5.916, p<0·001), which underscores the need for tailored therapeutic approaches within this subgroup. The observed outcome was influenced by a notably elevated ESR level with a median of 70 (IQR 37 to 88) compared to 66 (IQR 46 to 94), p=0·028), while no noteworthy distinction was found in the count of tender and swollen joints among the two cohorts. Additionally, visual analogue scale (VAS) results among the two age groups were found to be statistically significantly different (mean 5.64 (SD 2.654) versus 6.70 (SD 2.204), p<0.001). A smaller percentage of the population ≥ 60 were prescribed prednisolone compared with younger patients < 60 (30.8% compared to 69.2%, p=0·593), although there was no disparity in the quantity of preceding csDMARDs.

The patterns of treatment revealed variations in medication regimens. Elderly individuals were more likely to be administered biologic and targeted synthetic DMARDs as monotherapy in comparison with combination therapy (52.9% versus 47.1%). Moreover, the elderly had a higher likelihood of receiving biologic DMARDs over targeted synthetic DMARDs (88.5% versus 11.5%, p = 0.04), with non-TNF inhibitors more prevalent than TNF inhibitors (50.6% versus 37.9%). These findings suggest that age-related considerations may play a role in treatment selection. As reported by the Japan College of Rheumatology, the use of MTX in elderly patients necessitates comprehensive monitoring to minimize the potential for adverse events (Tanaka et al., 2016). Conversely, alternative csDMARDs and GCs are frequently used in the treatment of this specific patient population, likely due to the purportedly reduced occurrence of AEs compared to MTX (Mueller et al., 2014). The initial factor is a decrease in immune response as a result of the aging process. As a consequence of the age-related development of the immune system, an individual's diminishing immunological capacity to combat

infections poses a potential hazard for the emergence of infectious adverse events. The occurrence of rheumatoid arthritis itself additionally expedites the process of immunosenescence (Bauer, 2020). The second factor to consider is polypharmacy. As individuals grow older, there is a notable inclination towards polypharmacy (Charlesworth et al., 2015). The simultaneous intake of multiple medications amplifies the likelihood of adverse events due to drug interactions and complicates the management of diseases (Malik et al., 2023). The third aspect to consider pertains to the quantity of comorbid conditions. In elderly patients diagnosed with RA, the number of comorbid conditions tends to escalate. In a study conducted by Kawashima et al. (Kawashima et al., 2017) it was found that there is no substantial disparity in the occurrence of severe infections among patients with RA who are 65 years of age or older, regardless of whether they received biologic DMARDs or non-biologic DMARDs (Table I).

Treatment failure with biologic and targeted synthetic DMARDs

An analysis of treatment failure indicated an overall discontinuation rate of 12.96% (n=35), with inefficacy being the primary reason (65.71%) and adverse drug reactions (34.28%) being the other main reason for treatment failure. Persistence with biologic and targeted synthetic DMARDs therapy was greater in the population aged less than 60. Treatment failure in patients <60 was found to be higher compared to ≥60; all causes were 13.66% versus 11.49%, inefficiency was 9.3% versus 6.9%, and there was a similar chance of treatment failure due to adverse events (4.4%), highlighting the challenges in managing RA in this age group (Table 2). Overall, patients who received monotherapy or combination therapy with other csDMARDs, including sulfasalazine, hydroxychloroquine, or leflunomide, had a higher risk of treatment failure compared to those who received combination therapy with MTX with no statistically significant difference in hazard ratio; HR: 1·841 (95% CI: 0.746, 4.541), p=0·185. Upon examination of treatment discontinuation in different classes of DMARDs, overall, patients were less likely to discontinue therapy when prescribed targeted synthetic DMARDs compared to TNF inhibitor agents, although the finding was not significant. HR: 0.30 (95% CI: 0.90, 1·0.1), p=0·052. On further analysis, adjusting for confounding of interest, this difference showed to be significant: HR: 0.27 (0.070, 0.920), p<0·001.

Specifically, elderly individuals who received monotherapy had an even higher risk. However, in younger patients, this risk was found to be higher in other concomitant csDMARDs than monotherapy when compared with MTX combination therapy. Most investigations pertaining to the issue of biologic retention have emphasized that the concurrent use of MTX is a positive indicator of improved pharmaceutical durability. Various factors contribute to treatment failure, such as inefficacy and ADR. Patients achieve good clinical improvement with biologic and targeted synthetic DMARDs. However, the effectiveness of these medications can decrease over time (Fujii et al., 2024). In elderly individuals, the immunogenicity decreases because their immune system experiences a decline in its ability to generate antibody response (Accardi & Caruso, 2018; Bauer, 2020; Jani et al., 2014; Rocha et al., 2019). The phenomenon of immunogenicity has been widely acknowledged as a prevailing mechanism contributing to the diminished efficacy of biologic drugs after some time and leading to treatment failure (Rosenberg et al., 2023). Treatment failure can occur due to antidrug antibody production that is formed because of immune response to drugs with protein bases. These antibodies have the potential to neutralize the clinical effectiveness of these drugs. Combination of biologic drugs with MTX leads to reducing the elimination of medication by reducing the formation of antibodies against the medication, therefore the systemic exposure along with medication persistence of biologics will increase (Ancuta et al., 2016; Balsa et al., 2018; Danckert et al., 2024).

This study demonstrates a notable decline of 88% in the probability of treatment failure among the elderly receiving targeted synthetic DMARD therapy, which constitutes a compelling rationale for the efficacy of this medication class in comparison to TNF inhibitor therapy. Younger patients within this treatment category showed almost similar results, however, the reduced risk compared to TNF inhibitor therapy was not significant. Real-world data from drug based registry in Taiwan in 2018 (Hsieh, 2018) indicated that the persistence at the end of 12 months was comparable for individuals who began treatment with tofacitinib (88.5%) and those who started treatment with TNF inhibitors (90.8%).

Table I. Baseline characteristics of the patients

Characteristics	Total patients	< 60 years	≥ 60 years	p-value
Demographic characteristics				
Total patients	270 (100)	183 (67.8)	87 (32.2)	
Age, years., mean±SD	54.10±10.218	49.11±8.157	64.57±4.675	<0.001
Female	191 (70.7)	135 (73.8)	56 (64.4)	0.036
Smoking status				
Smoker	79 (29.3)	58 (31.7)	21 (24.1)	0.202
Non-smoker	191 (70.7)	125 (68.3)	66 (75.9)	
Clinical characteristics				
Disease duration, years, mean±SD	10.45±5.391	9.76±5.066	11.91±5.782	0.002
Seropositive RF	210 (77.8)	139 (76)	71 (81.6)	0.296
DAS28 ESR, mean±SD	5.862±1.130	5.916±1.100	6.748±1.190	0.254
SJC, mean±SD	7.28±6.487	7.17±6.414	7.51±6.670	0.696
TJC, mean±SD	8.25±6.729	8.33±7.026	8.08±6.093	0.774
VAS, mean±SD	6.36±2.405	6.70±2.204	5.64±2.654	<0.001
ESR, median (IQR)	66 (44, 91)	66 (46, 94)	70 (37, 88)	0.028
CRP, median (IQR)	22.30 (6.97, 45.17)	28.5 (10.1, 51)	13 (5.4, 38)	0.002
RDCI score ≥1	202 (74.8)	134 (73.2)	68 (78.2)	0.049
Comorbidities				
Osteoarthritis	123 (45.6)	87 (47.5)	36 (41.6)	0.342
Osteoporosis	56 (20.7)	38 (20.8)	18 (20.7)	0.989
Hypertension	132 (48.9)	73 (39.9)	59 (67.8)	<0.001
Diabetes mellitus	58 (21.5)	40 (21.9)	18 (20.7)	0.827
CKD	20 (7.4)	14 (7.7)	6 (6.9)	0.825
Anaemia	48 (17.8)	34 (18.6)	14 (16.1)	0.617
Depression	26 (9.6)	20 (10.9)	6 (6.9)	0.294
Respiratory diseases	72 (26.7)	49 (26.8)	23 (26.4)	0.538
Asthma	13 (4.8)	7 (3.8)	6 (6.9)	0.271
COPD	8 (3)	7 (3.8)	1 (1.1)	0.231
Lung fibrosis	51 (18.9)	35 (19.1)	16 (18.4)	0.885
Dyslipidaemia	50 (18.5)	33 (18)	17 (19.5)	0.766
Gastritis	25 (9.3)	19 (10.4)	6 (6.9)	0.356
Peptic ulcer	21 (7.8)	14 (7.7)	7 (8)	0.910
Treatment characteristics				
Previous biologic exposure				
Biologic naïve	148 (54.8)	99 (54.1)	49 (56.3)	0.732
Biologic experienced	122 (45.2)	84 (45.9)	38 (43.7)	
No. of previous biologics, mean±SD	0.64±0.822	0.69±0.868	0.55±0.711	0.202
Type of therapy				
Monotherapy	151 (55.9)	105 (57.4)	46 (52.9)	0.486
Combination therapy	119 (44.1)	78 (42.6)	41 (47.1)	

Values are given as n (%) unless otherwise specified by median (IQR) or mean (SD). Statistical imbalance tested χ^2 or Kruskal Wallis

A recent Canadian study reported that the rate of discontinuation of tofacitinib significantly reduced in patients who were older than 55 years in comparison to those who were younger than 45 years of age (Pope et al., 2020). Furthermore, a

recent Canadian study reported that the rate of discontinuation of tofacitinib significantly reduced in patients who were older than 55 years in comparison to those who were younger than 45 years of age (Pope et al., 2020).

Table II. Incidence rate and Cox proportional hazard estimates (95% CI) for b/tsDMARDs discontinuation.

Treatment Failure	**Total patients**	**< 60 years**	**≥ 60 years**
Number of subjects	270	183	87
Patients with treatment failure, n (%)	35 (12.96)	25 (13.66)	10 (11.49)
Reasons for treatment failure, n (%)			
Inefficiency	23 (65.71)	17 (9.3)	6 (6.9)
Adverse drug reactions	12 (34.28)	8 (4.4)	4 (4.6)
Others	2 (5.71)	1 (0.5)	1 (1.1)
Patients with TNF inhibitor failure, n (% of total population)	24 (8.88)	15 (62.5)	9 (37.5)
Reason for TNF inhibitor failure, n (%)			
- Inefficacy	16 (66.66)	11 (73.3)	5 (55.5)
- Adverse drug reactions	7 (29.16)	4 (26.6)	3 (33.3)
- Other	2 (8.33)	1 (6.6)	1 (11.1)
Patients with non-TNF inhibitor failure, n (% of total population)	9 (3.33)	7 (77.8)	2 (22.2)
Reason for non-TNF inhibitor failure, n (%)			
- Inefficacy	5 (55.55)	4 (57.1)	1 (50.0)
- Adverse drug reactions	4 (44.4)	3 (42.8)	1 (50.0)
Patients with tsDMARDs failure, n (% of total population)	3 (1.11)	3 (100)	0 (0)
Reason for tsDMARDs failure, n (%)			
- Inefficacy	2 (66.66)	2 (66.6)	0 (0)
- Adverse drug reactions	1 (33.33)	1 (33.3)	0 (0)
Hazard ratio (95% CI) (ref methotrexate)			
- Unadjusted:			
Non-MTX csDMARDs	1.67 (0.53, 5.18)	1.78 (0.517, 6.173)	1.44 (0.090, 23.13)
Monotherapy	1.84 (0.74, 4.54)	1.30 (0.494, 3.811)	4.26 (0.533, 34.09)
- Adjusted:			
Non-MTX csDMARDs	1.87 (0.58, 6.03)	2.14 (0.569, 8.067)	2.08 (0.120, 36.04)
Monotherapy	1.62 (0.64, 4.12)	1.40 (0.490, 4.014)	2.99 (0.351, 25.61)
Hazard ratio (95% CI) (ref TNF inhibitors)			
- Unadjusted:			
Non-TNF inhibitors	0.45 (0.20, 1.01)	**0.67 (0.271, 1.662)** *	0.13 (0.017, 1.090)
Targeted synthetic DMARDs	**0.30 (0.09, 1.01)** *	0.42 (0.121, 1.466)	**0.17 (0.082, 1.478)** *
- Adjusted:			
Non-TNF inhibitors	0.44 (0.19, 1.04)	0.63 (0.240, 1.674)	0.19 (0.023, 1.559)
Targeted synthetic DMARDs	**0.27 (0.07, 0.92)** *	0.36 (0.102, 1.331)	**0.12 (0.038, 1.265)** *

Table II. (Continued) Incidence rate and Cox proportional hazard estimates (95% CI) for b/tsDMARDs discontinuation.

Treatment Failure	**Total patients**	**< 60 years**	**≥ 60 years**
Hazard ratio (95% CI) (ref Tocilizumab)			
- Unadjusted:			
Etanercept	**3.51 (1.26, 9.78) ***	3.20 (0.985, 10.394)	4.68 (0.548, 40.127)
Golimumab	1.28 (0.25, 6.63)	1.53 (0.284, 8.479)	0.21 (0.032, 2.432)
Adalimumab	**3.54 (1.02, 12.24) ***	2.56 (0.575, 11.479)	7.91 (0.717, 87.33)
Infliximab	1.26 (0.14, 10.81)	1.19 (0.144, 1.329)	5.27 (0.330, 84.31)
Rituximab	2.13 (0.50, 0.30)	3.71 (0.830, 16.600)	0.098 (0.07, 1.021)
Certolizumab	1.51 (0.17, 12.95)	0.12 (0.092, 0.241)	11.45 (0.71, 183.58)
Tofacitinib	0.82 (0.19, 3.44)	0.91 (0.205, 4.084)	0.02 (0.121, 1.019)
- Adjusted:			
Etanercept	**3.87 (1.29, 11.60) ***	**3.66 (0.99, 13.42) ***	3.87 (0.425, 35.297)
Golimumab	1.84 (0.34, 10.00)	2.31 (0.385, 13.906)	0.01 (0.002, 0.089)
Adalimumab	**3.84 (1.04, 14.20) ***	3.97 (0.820, 19.299)	3.89 (0.314, 48.28)
Infliximab	1.63 (0.17, 15.05)	0.03 (0.092, 1.021)	8.10 (0.40, 162.27)
Rituximab	3.51 (0.77, 15.95)	**6.18 (1.19, 32.10) ***	0.07 (0.045, 1.001)
Certolizumab	1.90 (0.21, 16.92)	0.18 (0.011, 0.289)	13.98 (0.61, 320.41)
Tofacitinib	0.82 (0.18, 3.58)	0.95 (0.202, 4.531)	0.09 (0.021, 1.219)

In contrast to our findings, a Japanese study of the safety and efficacy of Golimumab in the elderly population observed that the rate of discontinuation for any cause within the six-month study period was 22.0% (n=925/4200) for younger individuals, while the corresponding rate for the elderly population was 25.3% (n=237/937) (Okazaki et al., 2018).

Treatment with non-TNF medications among the younger population was significantly associated with a 33% lower risk of treatment failure (p=0.047) before adjusting for confounders. However, after adjusting, the risk of treatment discontinuation was reduced further to 37% but did not remain significant. In elderly patients also we observed that non-TNF therapy was associated with an 87% reduction in treatment failure compared to TNF inhibitors therapy, although it was not significant. Our results are in accordance with prior published data from cohort studies. Results of the cohort study in the elderly Japanese population indicated that elderly patients with non-TNF inhibitor therapy had a lower risk of treatment discontinuation compared with patients with TNF inhibitor therapy HR 0.71 (95% CI: 0.59, 0.86), p<0.001 (Jinno et al., 2021).

Examining treatment discontinuation, caused by individual drugs in both groups showed that Etanercept and Adalimumab prescribed patients had a higher risk of treatment failure Etanercept: HR: 3.51 (95% CI: 1.26, 9.78), p=0·025; Adalimumab: HR: 3.54 (95% CI: 0.1.02, 12.24), p=0·012 which the risk of discontinuation increased after adjustment with statistically significant differences; Etanercept HR: 3.87 (95% CI: 1.29, 11.60), p=0·019; Adalimumab HR: 3.84 (95% CI: 1.04, 14.20), p=0·016, which calls for caution in prescribing these medications and underscores the importance of close monitoring and personalized treatment strategies. Patients ≥ 60 years old had a greater hazard ratio; HR: 4.68 (95% CI: 0.548, 40.127) compared with patients < 60 years old; HR: 3.20 (95% CI: 0.985, 10.394) with no statistically significant differences. After adjusting for confounding, the hazard ratio showed to increase to 7.91 in patients ≥ 60 taking Etanercept and 3.89 with Adalimumab. However, patients < 60 receiving Etanercept achieved a lower hazard ratio; HR: 2.56 (95% CI: 0.575, 11.479) and this value has increased in patients with Adalimumab; HR: 3.97 (95% CI: 0.820, 19.299) with an insignificant difference.

Multiple observational studies have shown that tocilizumab is related to enhanced drug retention and/or efficacy when compared to TNF inhibitor medications (Choy et al., 2017; Iannone et al., 2018; Lauper et al., 2018). One observational study compared treatment outcomes of Tocilizumab and TNF inhibitor medications among RA patients in twenty-six countries; 14.9% of patients who initiated tocilizumab administration experienced treatment discontinuation, while a corresponding proportion of 27.4% was observed among those who commenced TNF inhibitor therapy concluding longer drug survival in Tocilizumab therapy compared to TNF inhibitor medications during 1 year HR 1.15 (95% CI: 1.12, 1.19) vs HR 1.27 (95% CI: 1.24, 1.30) (Choy et al., 2017). Tocilizumab therapy was discontinued due to adverse events in 24.4% of the elderly group versus 17.5% of the young group, with the difference not being significant. Patients who discontinued the drug due to lack of efficacy tended to be fewer in the elderly group than in the young group (6.7% vs 14.3%) (Nakao et al., 2021). The observed conflict in results could potentially be attributed to the variation present among studies associated with the design of their research, achieved outcomes, and method used. In the elderly population, we have observed the approximate risk of 4 times higher compared to tocilizumab, however, it was found that adjusting for confounders of interest reduced the risk of discontinuation to 3 times which was not statistically significant. The younger population showed to have almost the same rate of discontinuation which increased after adjusting with a statistically significant difference Adjusted HR 3.66 (95% CI: 0.99, 13.42, p=0.011. Golimumab treatment in our study was revealed to have a protective effect against treatment discontinuation. This could be explained by a low proportion of elderly patients (14.3%) who received golimumab in combination with MTX and 50% of them received other csDMARDs combination.

CONCLUSION

In this study, we have contributed to the identification of each individual medication on treatment discontinuation with the impact of gender, disease duration, comorbidities using the RDCI score, smoking, DAS28 ESR, and corticosteroid use. This study showed that monotherapy with biologic or targeted synthetic DMARDs raises treatment failure risk, notably in older adults (≥60 years). Increased discontinuations due to ineffectiveness, but fewer adverse event-related discontinuations, contribute

to this risk. The elderly experience a lower percentage of failure due to both inefficacy and adverse events, suggesting better monotherapy tolerance in these individuals. The study identified medications impacting discontinuation, with targeted synthetic DMARDs emerging as potentially more suitable and secure for elderly RA patients than biologic DMARDs. Examining age-based discontinuation, rituximab significantly increased the risk, doubling after considering confounding factors. This could indicate that confounding factors, especially comorbidities and polypharmacy, smoking, corticosteroid use, and gender, exert a great impact on the risk of treatment failure among the elderly because of immunogenicity, which could lead to ADRs and diminish treatment efficacy.

The limitation of this study pertains to the restricted sample size, which precluded the execution of targeted analyses aimed at discerning the predictive factors underlying each distinct reason for treatment failure, including ADRs and inefficacy. To address this gap, future research endeavours should encompass larger sample sizes drawn from multiple centres, facilitating an in-depth investigation into treatment failures stemming from ADRs and inefficacy individually.

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CONFLICT OF INTEREST

The authors of this study declare no conflict of interest.

REFERENCES

Accardi, G., & Caruso, C. (2018). Immune-inflammatory responses in the elderly: an update. In (Vol. 15, pp. 1-4): Springer.

Ancuta, C., Pomirleanu, C., Belibou, C., Maxim, R., Petrariu, L., Strugariu, G., & Chirieac, R. (2016). THU0129 Clinical outcomes of immunogenicity in rheumatoid arthritis patients under anti-TNF biologics: results from an observational study. In: BMJ Publishing Group Ltd.

Ariyanti, D., Sauriasari, R., & Yunir, E. (2022). Evaluation of Current Practice of Antibiotic Use and Clinical Outcomes of Community-Acquired Pneumonia Patients with Type 2 Diabetes Mellitus in Indonesia. *Indonesian Journal of Pharmacy*, 583-591.

Balsa, A., Sanmarti, R., Rosas, J., Martin, V., Cabez, A., Gomez, S., & Montoro, M. (2018). Drug immunogenicity in patients with inflammatory arthritis and secondary failure to tumour necrosis factor inhibitor therapies: the REASON study. *Rheumatology*, *57*(4), 688-693.

Bauer, M. E. (2020). Accelerated immunosenescence in rheumatoid arthritis: impact on clinical progression. *Immunity & Ageing*, *17*(1), 6.

Busquets, N., Tomero, E., Descalzo, M. Á., Ponce, A., Ortiz-Santamaría, V., Surís, X.,...Gómez-Reino, J. J. (2011). Age at treatment predicts reason for discontinuation of TNF antagonists: data from the BIOBADASER 2.0 registry. *Rheumatology*, *50*(11), 1999-2004.

Charlesworth, C. J., Smit, E., Lee, D. S., Alramadhan, F., & Odden, M. C. (2015). Polypharmacy among adults aged 65 years and older in the United States: 1988–2010. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, *70*(8), 989-995. https://doi.org/https://doi.org/10.1093/gerona/glv013

Choy, E. H., Bernasconi, C., Aassi, M., Molina, J. F., & Epis, O. M. (2017). Treatment of Rheumatoid Arthritis With Anti–Tumor Necrosis Factor or Tocilizumab Therapy as First Biologic Agent in a Global Comparative Observational Study. *Arthritis care & research*, *69*(10), 1484-1494. https://doi.org/https://doi.org/10.1002/acr.23303

Danckert, N. P., Freidin, M. B., Granville Smith, I., Wells, P. M., Naeini, M. K., Visconti, A.,...Williams, F. M. (2024). Treatment response in rheumatoid arthritis is predicted by the microbiome: a large observational study in UK DMARD-naive patients. *Rheumatology*, keae045.

England, B. R., Sayles, H., Mikuls, T. R., Johnson, D. S., & Michaud, K. (2015). Validation of the rheumatic disease comorbidity index. *Arthritis care & research*, *67*(6), 865-872. https://doi.org/https://doi.org/10.1002/acr.22456

Filippini, M., Bazzani, C., Favalli, E. G., Marchesoni, A., Atzeni, F., Sarzi-Puttini, P.,...Gorla, R. (2010). Efficacy and safety of anti-tumour necrosis factor in elderly patients with rheumatoid arthritis: an observational

study. *Clinical reviews in allergy & immunology*, *38*, 90-96. https://doi.org/https://doi.org/10.1007/s12016-009-8142-1

Fujii, T., Murata, K., Onizawa, H., Onishi, A., Tanaka, M., Murakami, K.,...Hashimoto, M. (2024). Management and treatment outcomes of rheumatoid arthritis in the era of biologic and targeted synthetic therapies: evaluation of 10-year data from the KURAMA cohort. *Arthritis research & therapy*, *26*(1), 16.

Genevay, S., Finckh, A., Ciurea, A., Chamot, A. M., Kyburz, D., Gabay, C., & Arthritis, P. o. t. S. C. Q. M. P. f. R. (2007). Tolerance and effectiveness of anti–tumor necrosis factor α therapies in elderly patients with rheumatoid arthritis: A population-based cohort study. *Arthritis care & research*, *57*(4), 679-685. https://doi.org/https://doi.org/10.1002/art.22688

Hetland, M. L., Christensen, I. J., Tarp, U., Dreyer, L., Hansen, A., Hansen, I. T.,...Poulsen, U. E. (2010). Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, *62*(1), 22-32. https://doi.org/https://doi.org/10.1002/art.27227

Hsieh, S.-C. (2018). Real-world use of tofacitinib compared with tumor necrosis factor inhibitors in a cohort of 211 patients with rheumatoid arthritis: data from a drug-based registry study in Taiwan. 2018 ACR/ARHP Annual Meeting,

Hyrich, K., Watson, K., Silman, A., Symmons, D. P., & Register, B. B. (2006). Predictors of response to anti-TNF-α therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology*, *45*(12), 1558-1565. https://doi.org/https://doi.org/10.1093/rheumatology/kel149

Iannone, F., Ferraccioli, G., Sinigaglia, L., Favalli, E., Sarzi-Puttini, P., Atzeni, F.,...Farina, I. (2018). Real-world experience of tocilizumab in rheumatoid arthritis: sub-analysis of data from the Italian biologics' register GISEA. *Clinical rheumatology*, *37*, 315-321. https://doi.org/https://doi.org/10.1007/s10067-017-3846-8

Ishchenko, A., & Lories, R. (2016). Safety and Efficacy of Biological Disease-Modifying Antirheumatic Drugs in Older Rheumatoid Arthritis Patients: Staying the Distance. *Drugs & aging*, *33*(6), 387-398.

Jani, M., Barton, A., Warren, R. B., Griffiths, C. E., & Chinoy, H. (2014). The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. *Rheumatology*, *53*(2), 213-222. https://doi.org/https://doi.org/10.1093/rheumatology/ket260

Jinno, S., Onishi, A., Dubreuil, M., Hashimoto, M., Yamamoto, W., Murata, K.,...Ebina, K. (2021). Comparison of the drug retention and reasons for discontinuation of tumor necrosis factor inhibitors and interleukin-6 inhibitors in Japanese patients with elderly-onset rheumatoid arthritis—the ANSWER cohort study. *Arthritis research & therapy*, *23*(1), 1-9. https://doi.org/https://doi.org/10.1186/s13075-021-02496-w

Jourdain, H., Hoisnard, L., Sbidian, E., & Zureik, M. (2024). Persistence and safety of anti-TNF biosimilars versus originators in immune-mediated inflammatory diseases: an observational study on the French National Health Data System. *RMD open*, *10*(1), e003531.

Kawashima, H., Kagami, S.-i., Kashiwakuma, D., Takahashi, K., Yokota, M., Furuta, S., & Iwamoto, I. (2017). Long-term use of biologic agents does not increase the risk of serious infections in elderly patients with rheumatoid arthritis. *Rheumatology international*, *37*, 369-376. https://doi.org/https://doi.org/10.1007/s00296-016-3631-z

Krams, T., Ruyssen-Witrand, A., Nigon, D., Degboe, Y., Tobon, G., Fautrel, B.,...Constantin, A. (2016). Effect of age at rheumatoid arthritis onset on clinical, radiographic, and functional outcomes: the ESPOIR cohort. *Joint Bone Spine*, *83*(5), 511-515. https://doi.org/https://doi.org/10.1016/j.jbspin.2015.09.010

Kristin, E., Dinarti, L. K., Febrinasari, R., Pratiwi, W. R., Yasmina, A., & Jaya, S. I. (2023). Persistence to Antihypertensive and Clinical Outcomes in Acute Coronary Syndrome Patients after Percutaneous Coronary Intervention. *Indonesian Journal of Pharmacy*.

Lauper, K., Nordström, D. C., Pavelka, K., Hernández, M. V., Kvien, T. K., Kristianslund, E. K.,…Codreanu, C. (2018). Comparative effectiveness of tocilizumab versus TNF inhibitors as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis after the use of at least one biologic disease-modifying antirheumatic drug: analyses from the pan-European TOCERRA register collaboration. *Annals of the rheumatic diseases*, *77*(9), 1276-1282. https://doi.org/https://doi.org/10.1136/annrheumdis-2017-212845

Malik, M., Jones, B., Williams, E., Kurukulaaratchy, R., Holroyd, C., & Mason, A. (2023). Dual biologic therapy for the treatment of rheumatic diseases and asthma: a case series. *Rheumatology Advances in Practice*, *7*(1), rkad018.

Meraya, A. M., Alwhaibi, M., Syed, M. H., Shwihi, A., Mashraqi, M., Tripathi, R.,…Moraya, D. (2020). Utilization of psychotropic medications and polypharmacy among adults in Jazan Region, Saudi Arabia. *Indonesian Journal of Pharmacy*, *31*(3), 205-216.

Mueller, R. B., Kaegi, T., Finckh, A., Haile, S. R., Schulze-Koops, H., & von Kempis, J. (2014). Is radiographic progression of late-onset rheumatoid arthritis different from young-onset rheumatoid arthritis? Results from the Swiss prospective observational cohort. *Rheumatology*, *53*(4), 671-677. https://doi.org/https://doi.org/10.1093/rheumatology/ket399

Nakao, Y., Asanuma, Y. F., Wada, T. T., Matsuda, M., Yazawa, H., Yoshida, Y.,…Mimura, T. (2021). Efficacy, safety, and adherence of tocilizumab therapy in elderly patients with rheumatoid arthritis: A real-world observational study. *European Journal of Inflammation*, *19*, 20587392211045790.

Ochi, S., Mizoguchi, F., Nakano, K., & Tanaka, Y. (2021). Similarity of response to biologics between elderly-onset rheumatoid arthritis (EORA) and non-EORA elderly patients: from the FIRST registry. *The Journal of rheumatology*, *48*(11), 1655-1662.

Okazaki, M., Kobayashi, H., Shimizu, H., Ishii, Y., Yajima, T., & Kanbori, M. (2018). Safety, effectiveness, and treatment persistence of golimumab in elderly patients with rheumatoid arthritis in real-world clinical practice in Japan. *Rheumatology and therapy*, *5*, 135-148. https://doi.org/https://doi.org/10.1007/s40744-018-0101-y

Pope, J., Bessette, L., Jones, N., Fallon, L., Woolcott, J., Gruben, D.,…Haraoui, B. (2020). Experience with tofacitinib in Canada: patient characteristics and treatment patterns in rheumatoid arthritis over 3 years. *Rheumatology*, *59*(3), 568-574. https://doi.org/https://doi.org/10.1093/rheumatology/kez324

Radovits, B. J., Kievit, W., Fransen, J., van de Laar, M. A., Jansen, T. L., van Riel, P. L., & Laan, R. F. (2009). Influence of age on the outcome of antitumour necrosis factor alpha therapy in rheumatoid arthritis. *Annals of the rheumatic diseases*, *68*(9), 1470-1473. https://doi.org/https://doi.org/10.1136/ard.2008.094730

Rocha, S. d. B., Baldo, D. C., & Andrade, L. E. C. (2019). Clinical and pathophysiologic relevance of autoantibodies in rheumatoid arthritis. *Advances in Rheumatology*, *59*, 2.

Rosenberg, V., Chodick, G., Xue, Z., Faccin, F., & Amital, H. (2023). Real-World Data of Adherence and Drug Survival of Biologics in Treatment-Naïve and Treatment-experienced Adult Patients with Rheumatoid Arthritis. *Advances in therapy*, *40*(10), 4504-4522.

Silvagni, E., Bortoluzzi, A., Carrara, G., Zanetti, A., Govoni, M., & Scirè, C. A. (2018). Comparative effectiveness of first-line biological monotherapy use in rheumatoid arthritis: a retrospective analysis of the RECord-linkage On Rheumatic Diseases study on health care administrative databases. *BMJ open*, *8*(9), e021447.

Tanaka, Y., Harigai, M., Takeuchi, T., Yamanaka, H., Ishiguro, N., Yamamoto, K.,…Ishii, Y. (2016). Clinical efficacy, radiographic progression, and safety through 156 weeks of therapy with subcutaneous golimumab in combination with

methotrexate in Japanese patients with active rheumatoid arthritis despite prior methotrexate therapy: final results of the randomized GO-FORTH trial. *Modern Rheumatology*, *26*(4), 481-490. https://doi.org/https://doi.org/10.3109/14397595.2015.1109762

Yun, H., Xie, F., Delzell, E., Chen, L., Yang, S., Saag, K. G.,...Curtis, J. R. (2015). The comparative effectiveness of biologics among older adults and disabled rheumatoid arthritis patients in the Medicare population. *British journal of clinical pharmacology*, *80*(6), 1447-1457.

Zeng, K., Zhou, E., Ren, T., Yin, Y., He, M., Long, X.,...Wu, J. (2023). Efficacy and safety of Tofacitinib in treating the elderly rheumatoid arthritis. *Chinese Journal of Geriatrics*, 40-45.