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Real-world persistence of initial targeted therapy strategy in monotherapy versus combination therapy in patients with chronic inflammatory arthritis

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Abstract

Objective: The persistence of biologic (b) and targeted synthetic (ts) disease-modifying antirheumatic drugs(DMARDs) in monotherapy versus in combination with conventional synthetic (cs) DMARDs is still a controversial topic in

Abbreviations: AS, ankylosing spondylitis; B, biologics; CI, confidence interval; Cs, conventional synthetic; DMARDs, disease-modifying antirheumatic drugs; HR, hazard ratio; IRR, incidence rate ratio; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNFi, TNF-inhibitor; Ts, targeted synthetic.

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rheumatic diseases. To clarify this issue, the retention of the initial treatment strategy of b/tsDMARD in combination with csDMARD versus monotherapy in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) patients under real-life conditions was evaluated. Factors associated with maintenance of the initial strategy were analysed.

Methods: Nested cohort study within the Spanish BIOBADASER III registry. Bivariate comparisons and multivariate Cox proportional hazards models were used for the analyses.

Results: A total of 2521 patients were included in the study. In the multivariate model, the initial strategy of combination therapy was associated with shorter persistence in patients with RA (hazard ratio [HR] 1.58;95% confidence interval [CI] 1.00–2.50; $p = .049$), PsA (HR 2.48; 95% CI 1.65–3.72) and AS (HR 16.77; 95% CI 7.37–38.16; $p < .001$), regardless of sex, time of disease progression, baseline disease activity, glucocorticoid use or type of b/tsDMARD. Overall, the combination strategy was associated with an increased incidence of adverse events (incidence rate ratio [IRR] 1.13; 95% CI 1.05–1.21).

Conclusions: In this real-life study, the strategy of combining a b/tsDMARD with a csDMARD is associated with lower persistence and worse safety profile compared to monotherapy in RA and especially in PsA and AS, suggesting that combination therapy should be rethought as first choice in RA patients, but especially in PsA and AS patients.

KEYWORDS
ankylosing spondylitis, antirheumatic agents, biologic therapy, psoriatic arthritis, rheumatoid arthritis

1 | INTRODUCTION

Clinical practice guidelines for the management of rheumatoid arthritis (RA) recommend that when a biologic (b) disease-modifying antirheumatic drug (DMARD) is indicated, it should be used in combination with a conventional synthetic (cs) DMARD due to the improved efficacy and reduced immunogenicity of the combination.[1] A recent systematic review of 44 randomized clinical trials concluded that the combination of a bDMARD or targeted synthetic (ts) DMARD with a csDMARD was generally more effective than b/tsDMARD monotherapy, both in naïve and in an inadequate response to csDMARD in RA patients.[2] However, in clinical practice, up to 30% of patients with RA are treated with bDMARD in monotherapy,[3–6] possibly because of csDMARD's intolerance, contraindications, or patient preference. Assessing the persistence of treatments in the real world is particularly useful, as it is considered an indirect marker not only of their safety and efficacy, but also of patient satisfaction.[7,8] Several studies using registries and other real-world sources of information have consistently shown that, overall, concomitant use of bDMARD and csDMARD is associated with a higher likelihood of

Key Messages

- This analysis compared the persistence of the initial targeted therapy strategy in monotherapy versus combined with csDMARDs.
- Combination strategy is associated with shorter persistence and worse safety profile than monotherapy in chronic inflammatory arthritis.
- Monotherapy should be considered as first choice in RA, but especially in PsA and AS patients.

bDMARD persistence.[3,5,9–12] Moreover, in a systematic review of 98 studies that used information from registries or health care databases and included over 200,000 patients with RA, the concomitant use of a csDMARD was a significant predictor of a lower likelihood of bDMARD discontinuation.[13] However, there may be some differences among bDMARDs; thus, a study using tocilizumab registries showed no differences in terms of drug persistence between tocilizumab in monotherapy and in combination with a csDMARD, while the combination of a TNF-inhibitor (TNFi) with a csDMARD was associated with a lower likelihood of treatment discontinuation compared to TNF-inhibitor monotherapy.[10]

In patients with psoriatic arthritis (PsA), when a bDMARD is considered indicated, there is no conclusive recommendation on the concomitant use of a csDMARD, with this being considered part of the research agenda for the management of PsA.[14] Although treatment patterns seem to vary over time, the use of biologic monotherapy is also common among patients with PsA.[6,15] A systematic review of six randomized controlled trials found that concomitant use of methotrexate (MTX) with a TNFi is not associated with a clear beneficial effect compared to TNFi monotherapy, except for some data suggesting that the combination may reduce the progression of structural damage.[16] The results from registries and other observational sources regarding the impact of combination therapy on drug persistence show inconsistent results. Some studies have shown no difference between combination therapy and monotherapy[17–20]; others suggest that bDMARD persistence is better when adding a csDMARD.[9,21–24]

According to clinical practice guidelines, in adult patients with ankylosing spondylitis (AS), despite treatment with NSAIDs, treatment with a TNFi over no treatment with a TNFi is strongly recommended, but, although with a low level of evidence, the guidelines recommend against the coadministration of MTX.[25] Information from registries or observational studies on biologic persistence in patients with AS is very limited and shows somewhat inconsistent results, but most studies show no impact of adding MTX to the TNFi,[22,26,27] while only one study indicates a higher persistence of the TNFi in those patients receiving concomitant MTX.[9]

To our knowledge, very few studies have compared the persistence of b/tsDMARD using the same source of patients and the same methodology, and none of them have evaluated the survival of the initial target therapy strategy: monotherapy or combined in patients with RA, PsA or AS under real-life conditions. The primary objective of this study was to determine factors associated with potential differences in the persistence of the initial targeted therapy strategy with (combination strategy) versus without (monotherapy strategy) csDMARDs in patients with these three clinical conditions in a real-world clinical setting.

2 | PATIENTS AND METHODS

2.1 | Study design and patient population

This is a nested cohort study within a registry based on routine clinical data. The original study is BIOBADASER III, a prospective Spanish registry with 28 participating centres that was established at the end of 2015 to evaluate the long-term safety and effectiveness of patients with rheumatic diseases diagnosed based on clinical grounds who are undergoing treatment with targeted therapy: bDMARD, including biosimilars and tsDMARD.[28] The BIOBADASER III registry is supported by the Spanish Agency of Medicines (https://www.aemps.gob.es/en/home.htm), the Spanish Society of Rheumatology (https://www.ser.es/) and by most of the pharmaceutical companies with b/tsDMARD in the Spanish market. Adult patients with a diagnosis of RA, PsA (peripheral and mixed forms) or AS (patients with non-radiographic axial SpA were not included in this study) on active follow-up and who initiated and maintained for at least 3 months treatment with a targeted therapy using a combination strategy or monotherapy were included in this study. The inclusion period was from December 2015 to October 15, 2020.

The information in BIOBADASER is collected during the patient's visits to the rheumatology clinics. The information is included in the database at baseline (defined as the time of initiating treatment with a targeted therapy), when an adverse effect or a change in treatment with the biologic occurs, and for effectiveness assessment, at least once per year (follow-up visit). Data are also recorded in the case of death for any reason or b/tsDMARD discontinuation for any cause.

The project was approved by the Ethics Review Committee of the Hospital Universitario Clinic Barcelona, which acted as the reference committee (approval code FER-ADA-2015-01). Written informed consent was obtained from all participants.

2.2 | Exposure, outcomes and covariates

The combination therapy strategy was defined as initiating a b/tsDMARD and a concomitant csDMARD simultaneously and monotherapy strategy was defined as initiating b/tsDMARD therapy without the addition of a concomitant csDMARD. The main variables were treatment strategy start date (the date when the patient started b/tsDMARD therapy, either in monotherapy or

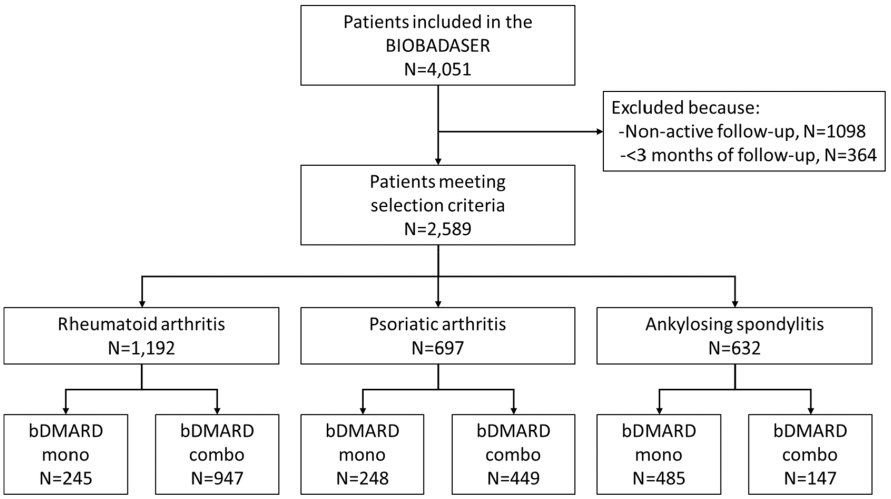

FIGURE 1 Flow-chart. Patients included in the analysis. bDMARD, biologic disease-modifying antirheumatic drug; combo, combination therapy; mono, monotherapy.

in combination) and treatment discontinuation date (the date when the patient changed treatment strategy from combination to monotherapy or viceversa) or if the patient stop the target therapy.

The primary outcome was persistence of treatment strategy, defined as the time elapsed from the date of initiation of b/tsDMARD in monotherapy or in combination until discontinuation of the initial strategy. After therapy initiation, patients who were switched to a different drug from the same class (b/tsDMARD or csDMARD) but maintained the initial strategy (combination or monotherapy) were considered to persist on the strategy.

The covariates included age at the time of initiating the first b/tsDMARD, sex, cotreatment with a csDMARD (yes/no), cotreatment with glucocorticoids (yes/no) diagnosis, use of TNFi as initial biologic (yes/no), disease duration to initiating treatment with a b/tsDMARD and disease activity as assessed by DAS28 or BASDAI.

2.3 | Statistical analysis

Quantitative variables are described with the mean and standard deviation or the median and interquartile range, and qualitative variables are described with the absolute and relative frequencies. For baseline comparisons, quantitative variables were compared using Student's *t*-test, nonparametric variables were compared with the Mann–Whitney *U* test or the Kruskal–Wallis *H* test, and qualitative variables were compared using the chi-squared test or Fisher's exact test.

The persistence of b/tsDMARD was analysed separately in RA, PsA and AS patients using the Kaplan–Meier method and compared between monotherapy and combination groups with the log-rank test. Multivariate Cox proportional hazard models were constructed with b/tsDMARD persistence as the outcome. Age, disease duration and disease activity at the start of the targeted therapy, as continuous variables, and sex, initial use of TNFi, glucocorticoids and combination therapy, as categorized variables were considered covariates. In the multivariate model were included the covariates which showed a p value <.20 in a bivariate Cox regression analysis, together with those considered clinically relevant (sex). Four multivariate models were constructed: a global model with all patients and including diagnosis as a covariate, and a model for RA, PsA and AS diagnoses.

All statistical analyses were performed using STATA software, version 16.0 SE (Stata Corporation). The results were considered significant at $p < .05$.

3 | RESULTS

3.1 | Patient disposition and characteristics

Of the 4051 patients included in the BIOBADASER registry, 2521 met the selection criteria and were included in this study; 47.2% ($n = 1192$) of them were diagnosed with RA, and the remaining were almost evenly distributed between PsA (27.6%, $n = 697$) and AS (25.1%, $n = 632$) (see flow-chart in Figure 1). b/tsDMARD monotherapy was used as the initial strategy in 20.5% ($n = 245$) of the patients with RA, 35.6% ($n = 248$) of patients with PsA and in 76.7% ($n = 485$) of the patients with AS. The median (interquartile range) duration of the initial treatment strategy (either monotherapy or combination) was 20 (12–32) months for patients with RA, 22 (12–40) months for patients with PsA, and 24 (14–43) months for patients with AS.

The characteristics of the patients are shown in Table 1. The monotherapy and combination therapy groups were

TABLE 1 Baseline characteristics of the patients included in the analysis.

	Rheumatoid arthritis			Psoriatic arthritis			Ankylosing spondylitis			Total		
	N = 1192			*N* = 697			*N* = 632			*N* = 2521		
Variable (%)	Mono *N* = 245 (20.5)	Combo *N* = 947 (79.5)	*p* value	Mono *N* = 248 (35.6)	Combo *N* = 449 (64.4)	*p* value	Mono *N* = 485 (76.7)	Combo *N* = 147 (23.3)	*p* value	Mono *N* = 978 (38.8)	Combo *N* = 1543 (61.2)	*p* value
Age at b/tsDMARD initiation (years), mean ± SD	58.31 ± 2.6	55.3 ± 12.3	<.001	51.3 ± 12.2	49.9 ± 11.3	.122	45.6 ± 12.9	48.0 ± 14.3	.053	50.2 ± 13.7	53.1 ± 12.6	<.001
Sex (females), *n* (%)	204 (83.3)	712 (75.2)	.008	130 (52.4)	236 (52.6)	.971	146 (30.1)	49 (33.3)	.458	480 (49.1)	997 (64.6)	<.001
DAS28	4.7 (1.2)	4.8 (1.3)	.375	4.9 (2.6)	4.9 (2.7)	.945				4.2 (1.3)	4.6 (1.3)	<.001
BASDAI				4.1 (1.2)	4.2 (1.2)	.490	5.6 (2.1)	5.4 (2.3)	.400	5.5 (2.2)	5.3 (2.4)	.200
Disease duration (years), median [IR]	5.3 [2.3–9.7]	4.4 [1.8–9.5]	.203	3.1 [1.1–8.0]	3.1 [1.1–6.9]	.4543	2.5 [0.7–10.0]	3.5 [1.0–9.8]	.2625	3.5 [1.0–9.5]	3.9 [1.5–8.5]	.0926
First b/tsDMARD, *n* (%)[a]												
TNFi	94 (13.1)	621 (86.9)	<.001	132 (27.6)	346 (72.4)	<.001	416 (75.2)	137 (24.8)	.04	642 (36.8)	1104 (63.2)	<.001
Anti-IL6	52 (42.3)	71 (57.7)								52 (42.3)	71 (57.7)	
Anti-B-cell (CD20)	13 (18.8)	56 (81.2)								13 (18.8)	56 (81.2)	
JAKi	56 (35.0)	104 (65.0)		4 (57.1)	3 (42.9)					60 (35.9)	107 (64.1)	
Anti-IL1	1 (50.0)	1 (50.0)								1 (50.0)	1 (50.0)	
Anti-IL17A				40 (46.5)	46 (53.5)		67 (88.2)	9 (11.8)		107 (66.1)	55 (34.0)	
Anti-IL12/23				17 (47.2)	19 (52.8)		2 (66.7)	1 (33.3)		19 (47.5)	20 (52.5)	
PDE4i				55 (61.1)	35 (38.9)					55 (61.1)	35 (38.9)	
Abatacept	29 (23.6)	94 (76.4)								29 (23.6)	94 (76.4)	
Glucocorticoids (yes), *n* (%)	147 (60.0)	612 (64.6)	.845	63 (69.2)	149 (70.3)	.855	22 (4.5)	44 (29.9)	<.001	232 (23.7)	805 (52.2)	<.001

[a]Percentages were calculated by row.

Abbreviations: bDMARD, biologic disease-modifying antirheumatic drug; IL, interleukin; JAKi, Janus kinase inhibitor; PDE4i, phosphodiesterase 4 inhibitor; SD, standard deviation; TNFi, tumour necrosis factor inhibitor.

generally well-balanced regarding age and sex for PsA and AS; however, patients with RA in the monotherapy group were older and more likely to be female than patients in the combination group. Disease duration was similar between the monotherapy and combination groups in patients with RA, PsA and AS, showing PsA patients a trend toward longer disease duration in monotherapy with respect to the combination strategy. With respect to disease activity at the start of biologic therapy, DAS28 in patients with RA and PsA and BASDAI in AS were similar in both types of strategies (Table 1). The most frequent initial targeted therapy was a TNFi ($n = 1745$, 69.2%); when a TNFi was prescribed, it was more frequently used in combination with a csDMARD in RA patients (87%, $n = 621$ vs. 13%, $n = 93$ for the combination and monotherapy groups, respectively) and PsA patients (72.4%, $n = 346$ vs. 27.6%, $n = 132$ for the combination and monotherapy groups, respectively) but more frequently prescribed as monotherapy in patients with AS (24.8%, $n = 137$ vs. 75.2%, $n = 416$ for the combination and monotherapy groups, respectively). The proportion of patients who were receiving glucocorticoids was higher in the combination group than in the monotherapy group (52.2% vs. 23.7%), especially among patients with AS (29.9% vs. 4.5%).

3.2 | Strategy persistence

Unadjusted survival analysis showed that the persistence of b/tsDMARD in monotherapy or combination therapy was not significantly different in patients with RA (Figure 2A). However, in patients with PsA (Figure 2B) and those with AS (Figure 2C), the strategy of using b/tsDMARD in monotherapy showed significantly longer survival than the combination strategy (log-rank test $p < .001$ for both comparisons).

Overall, in a global multivariate model, there were no differences in the persistence of the initial treatment strategy depending on the clinical entity (Table S1). Thus, compared to RA patients, the likelihood of treatment strategy persistence was not significantly different in patients with PsA (HR 1.06, 95% CI 0.80–1.40, $p = .677$) or patients with AS (HR 1.48, 95% CI 0.99–2.20, $p = .053$). Regarding treatments, the use of TNFi compared to other bDMARD was associated with a longer persistence (HR 0.74, 95% CI 0.58–0,94, $p = .016$), while glucocorticoids were associated with a shorter persistence (1.36 95% CI 1.02–1.82, $p = .037$). In this global model, the b/tsDMARD combination therapy strategy was associated with a shorter persistence than the monotherapy strategy (HR 3.04, 95% CI 2.14–4.32, $p < .001$).

When analysed by clinical entities in the multivariate model, compared to monotherapy, the combination therapy was associated with shorter b/tsDMARD persistence in patients with RA (HR 1.58, 95% CI 1.00–2.50, $p = .049$), PsA (HR 2.48, 95% CI 1.65–3.72, $p < .001$) and AS (HR 16.77, 95% CI 7.37–38.16, $p < .001$) (Table 2). Other factor significantly associated with longer b/tsDMARD persistence was the age at treatment initiation among patients with RA (HR 0.98, 95% CI 0.97–0.99, $p = .004$) (Table 2). Interestingly, neither disease activity nor TNFi or glucocorticoid use at the initiation of targeted therapy was associated with persistence of the initial therapeutic strategy.

3.3 | Safety profile

The frequency of adverse events for the whole group of combination therapy compared to the group who received b/tsDMARD monotherapy is presented in Table 3. Overall, the incidence of any adverse event in the combination group significantly increased by 13% (the incidence rates [IR] were 281 and 250 cases per 1000 patient-years in the combination and monotherapy groups, respectively; $p = .001$), but the rate of serious adverse events did not differ between the study groups (IR 35 and 34 cases per 1000 patient-years in the combination and monotherapy groups, respectively; $p = .857$). Most groups of adverse events occurred more frequently among patients who received a targeted therapy in combination, although the differences were statistically significant only for 'infections and infestations' (incidence rate ratio [IRR] 1.21, 95% CI 1.05–1.40) and 'musculoskeletal and connective tissue disorders' (IRR 1.67, 95% CI 1.10–2.53). The incidence rates of 'immune system disorders' and 'neoplasms benign, malignant and unspecified' were 24% and 19%, respectively, higher in the combination group than in the monotherapy group, but the differences were not statistically significant.

4 | DISCUSSION

The most important findings of this manuscript can be summarized as follows: (1) Under real-world conditions, the strategy of combining a targeted therapy with a csDMARD was associated with shorter treatment persistence in RA and especially in PsA and AS compared to a monotherapy strategy; (2) in the multivariable analysis, none of the factors studied including age, sex, time of disease evolution, initial disease activity, use of glucocorticoids, or type of targeted therapy, were associated with worse persistence of the initial strategy; and (3) overall, the combination strategy showed a worse safety profile than the monotherapy strategy.

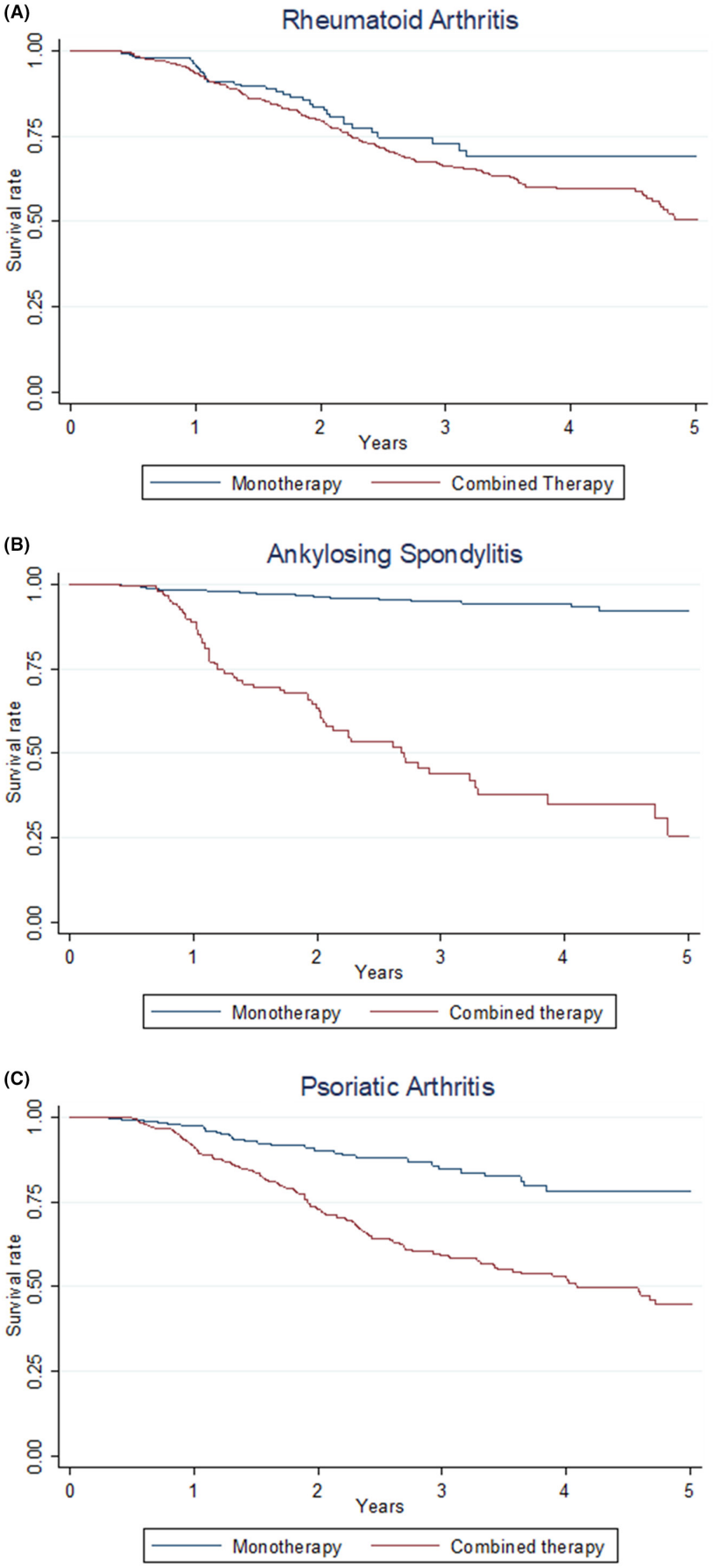

FIGURE 2 Biologic disease-modifying antirheumatic drug treatment strategy persistence (Kaplan–Meier plots).

The main objective of this work was to analyse patient and disease characteristics associated with persistence on initial targeted therapy strategy, either as monotherapy or in combination with csDMARD, in RA, PsA and AS patients using a national registry database under real-world conditions. The pattern of b/tsDMARD use in routine clinical practice shown in our study is somewhat consistent with clinical practice guideline recommendations. For example, b/tsDMARD monotherapy is more commonly used in patients with AS, where guidelines discourage the use of combination therapy,[25] and less commonly used in patients with RA, where guidelines recommend combination therapy.[1] However, despite the guideline recommendations, in our series 20% of RA patients (245 of 1192) initiated b/tsDMARD as monotherapy in real-world conditions.

To the best of our knowledge, few studies have analysed the impact of the combination with a csDMARD on b/tsDMARD persistence in these three clinical entities using the same source of real-world data.[9,22,29,30] George et al., in a retrospective study, showed that the use of MTX in combination with a TNFi increased the persistence of the TNFi in patients with RA (HR 0.85, 95% CI 0.80–0.89), patients with PsA (HR 0.81, 95% CI 0.74–0.89) and patients with AS (HR 0.79, 95% CI 0.67–0.93).[9] The inconsistency between their results and ours could be explained in part by differences in methodology. George et al. used a United States administrative claims database from nationally representative private health care insurance.[9] Administrative databases were not originally conceived for research purposes, and although they have some advantages, they also have

TABLE 2 Factors associated with targeted treatment initial strategy discontinuation in the bivariate and multivariate analyses by clinical entity.

	Bivariate			Multivariate		
Rheumatoid arthritis	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age at b/tsDMARD initiation (years)	0.98	(0.97–0.99)	<.001	0.98	(0.97–0.99)	.004
Sex (male)	1.09	(0.82–1.46)	.553	1.03	(0.73–1.45)	.859
Disease duration (years)	0.98	(0.96–1.00)	.018	–	–	–
DAS28	1.01	(0.91–1.11)	.892	–	–	–
TNFi (other b/tsDMARD)	0.95	(0.75–1.21)	.685	–	–	–
Glucocorticoids (No)	1.46	(0.90–2.39)	.128	1.47	(0.90–2.40)	.128
Combination (Monotherapy)	1.34	(0.95–1.90)	.095	1.58	(1.00–2.50)	.049
Psoriatic arthritis						
Age at b/tsDMARD initiation (years)	0.99	(0.97–1.01)	.027	0.99	(0.98–1.0)	.097
Sex (male)	0.87	(0.65–1.17)	.351	0.94	(0.70–1.27)	.694
Disease duration (years)	0.98	(0.95–1.00)	.290	–	–	–
DAS28	1.01	(0.89–1.16)	.840	–	–	–
TNFi (other bDMARD)	1.08	(0.78–1.51)	.638	–	–	–
Glucocorticoids (no)	1.73	(1.09–2.73)	.019	1.55	(0.98–2.46)	.059
Combination (monotherapy)	2.53	(1.69–3.79)	<.001	2.48	(1.65–3.72)	<.001
Ankylosing spondylitis						
Age at bDMARD initiation (years)	1	(0.98–1.02)	.911	0.98	(0.96–1.00)	.114
Sex (male)	0.74	(0.45–1.21)	.225	0.48	(0.21–1.10)	.082
Disease duration (years)	0.99	(0.97–1.01)	.432	–	–	–
BASDAI	0.99	(0.90–1.10)	.909	–	–	–
TNFi (other bDMARD)	1.72	(0.75–3.95)	.202	–	–	–
Glucocorticoids (no)	2.05	(1.15–3.68)	.015	0.62	(0.33–1.15)	.132
Combination (monotherapy)	13.58	(8.28–22.28)	<.001	16.77	(7.37–38.16)	<.001

Abbreviations: b/tsDMARD, biologic/targeted synthetic disease-modifying antirheumatic drug; CI, confidence interval; HR, hazard ratio; TNFi, tumour necrosis factor inhibitors.

TABLE 3 Adverse events overall and by System Organ Class (MedDRA).

Adverse event	Incidence rate (95% CI) (cases per 1000 patient-years)		Incidence rate ratio	95% CI	*p* value
	Combination	Monotherapy			
Overall					
Any adverse event	280.70 (268.30–293.70)	250.20 (236.70–264.50)	1.13	(1.05–1.21)	.001
Serious adverse events	34.60 (30.40–39.30)	34.00 (29.30–39.60)	1.02	(0.84–1.24)	.857
System Organ Class					
Infections and infestations	76.30 (70.00–83.20)	63.10 (56.40–70.40)	1.21	(1.05–1.40)	.007
Gastrointestinal disorders	38.60 (34.20–43.60)	36.30 (31.30–42.00)	1.07	(0.88–1.29)	.501
General disorders and administration site condition	16.50 (13.70–19.90)	13.70 (10.80–17.40)	1.21	(0.90–1.64)	.214
Skin and subcutaneous tissue disorders	5.50 (4.00–7.60)	4.60 (3.10–7.00)	1.11	(0.79–1.55)	.555
Injury, poisoning and procedural complications	12.20 (9.80–15.20)	11.90 (9.20–15.30)	1.03	(0.74–1.44)	.858
Nervous system disorders	10.10 (8.00–12.90)	10.70 (8.20–14.00)	0.95	(0.66–1.36)	.787
Complementary examinations	4.50 (3.10–6.40)	4.60 (3.10–7.00)	0.97	(0.56–1.67)	.905
Cardiac disorders	7.90 (6.00–10.30)	9.30 (6.90–12.40)	0.85	(0.58–1.27)	.436
Renal and urinary disorders	5.20 (3.70–7.30)	3.80 (2.40–6.00)	1.37	(0.78–2.39)	.273
Surgical and medical procedures	10.10 (8.00–12.90)	8.50 (6.30–11.40)	1.20	(0.82–1.76)	.351
Blood and lymphatic system disorders	7.90 (6.00–10.30)	5.40 (3.70–7.90)	1.46	(0.92–2.31)	.112
Metabolism and nutrition disorders	5.20 (3.70–7.30)	4.00 (2.60–6.20)	1.30	(0.75–2.25)	.352
Musculoskeletal and connective tissue disorders	10.70 (8.50–13.50)	6.40 (4.60–9.10)	1.67	(1.10–2.53)	.016
Immune system disorders	9.20 (7.20–11.80)	7.50 (5.40–10.30)	1.24	(0.83–1.87)	.295
Eye disorders	8.60 (6.70–11.20)	12.30 (9.60–15.80)	0.71	(0.49–1.01)	.057
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5.50 (4.00–7.60)	4.60 (3.10–7.00)	1.19	(0.71–2.01)	.506
Respiratory, thoracic and mediastinal disorders	14.00 (11.40–17.10)	10.90 (8.30–14.20)	1.29	(0.92–1.80)	.134
Vascular disorders	4.00 (2.80–5.90)	3.20 (2.00–5.30)	1.25	(0.67–2.32)	.476
Hepatobiliary disorders	5.10 (3.60–7.10)	4.20 (2.80–6.50)	1.20	(0.70–2.07)	.509
Ear and labyrinth disorders	4.60 (3.20–6.60)	5.80 (4.10–8.40)	0.79	(0.48–1.32)	.369
Endocrine disorders	2.80 (1.80–4.40)	2.60 (1.50–4.50)	1.08	(0.54–2.20)	.822
Psychiatric disorders	3.40 (2.30–5.20)	3.60 (2.30–5.80)	0.95	(0.51–1.76)	.865

(Continues)

TABLE 3 (Continued)

Adverse event	Incidence rate (95% CI) (cases per 1000 patient-years)		Incidence rate ratio	95% CI	*p* value
	Combination	Monotherapy			
Pregnancy, puerperium and perinatal conditions	1.60 (0.90–3.00)	3.40 (2.10–5.50)	0.48	(0.22–1.02)	.058
Congenital, familial and genetic disorders	0.70 (0.30–1.80)	0.80 (0.30–2.10)	0.93	(0.25–3.45)	.910
Reproductive system and breast disorders	2.20 (1.30–3.70)	1.60 (0.80–3.20)	1.39	(0.59–3.28)	.451

Abbreviations: CI, confidence interval, MedDRA, the Medical Dictionary for Regulatory Activities.

several limitations for clinical research, including problems with the identification of cases[31–33]; therefore, if available, clinical registries are preferred over an administrative database for clinical research.[31] However, using a Norwegian DMARD registry, Heiberg et al. in the bivariate analysis found that combination therapy was significantly superior in terms of bDMARD persistence in patients with RA or PsA but not in patients with AS; overall, in contrast to our results, in a multivariate model for the whole sample, combination therapy was associated with longer b/tsDMARD persistence than b/tsDMARD monotherapy.[22] It is important to note that this Norwegian study only analysed 1-year retention rates.[22] The other two studies, conducted using clinical registries, did not provide results regarding retention rates for the specific diseases, but in both cases, when analysing the sample as a whole, the combination of the bDMARD with a csDMARD was not associated with longer bDMARD persistence.[29,30] A key difference between our study and others is that we defined monotherapy as a global strategy; that is, patients who initiated treatment with a b/tsDMARD in monotherapy and who were also switched to another b/tsDMARD in monotherapy were considered to remain on monotherapy. In our view, this definition could be a major factor for explaining the differences between our results and those of previous studies. Contrary to intuition, under real-world conditions, disease activity at initiation of targeted therapy was not associated with a preference for initial use of combination therapy or with a change in initial treatment strategy during follow-up. While RA patients initiating monotherapy were significantly older than those initiating combination therapy, and although age was associated with higher persistence in univariate analysis, multivariate analysis showed that monotherapy was associated with better persistence after adjustment for patient age. Regarding glucocorticoids, although they are generally used in more symptomatic RA patients, it is reasonable to assume that their use should be associated with less persistence with standard therapy. However, in our series, the use of glucocorticoids in patients with RA was not associated with changes in the persistence of the initial therapeutic strategy.

Importantly, none of the abovementioned studies reported data on the safety of the combination strategy compared to b/tsDMARD monotherapy. We found that the addition of a csDMARD to a b/tsDMARD is associated with significantly worse safety profile than b/tsDMARD in monotherapy. The greatest increase in adverse events was observed for 'infections and infestations' (21% increase over monotherapy) and especially 'musculoskeletal and connective tissue disorders' (67% increase over monotherapy). These adverse events are consistent with the known safety profile of DMARD.[34] It is important to highlight that in our safety analysis, we did not control for any risk factors, and there was no control for multiplicity; therefore, our results for specific adverse events should be taken with caution. Overall, however, our results show that the strategy of combining a b/tsDMARD with a csDMARD poses safety issues, suggesting that the poorer persistence of this strategy is related to poorer safety profile.

In addition to the issue of multiplicity, our study has the limitation of not including other factors that in previous studies have been associated with b/tsDMARD persistence in patients with these conditions, such as smoking status, baseline comorbidity, global health, functional status or C-reactive protein, although the role of these factors is not consistent across studies.[5,17,18,23,24,29] Therefore, the presence of residual confounding could have biased our results. Other limitations of our study include the lack of information on prior use of csDMARDs and the reason for initiating b/tsDMARDs, data not collected in BIOBADASER. Patients with RA are more susceptible to infections than patients with PsA and AS. This fact should be considered when interpreting the higher incidence of infections in patients on combination therapy found in our study, as it might be influenced by the fact that most of the patients analysed were RA patients on combination

therapy. In addition, the influence that patient-physician shared decision making may have had on the change in initial b/tsDMARD treatment strategy during follow-up is an important factor that was not considered in our analysis. Although drug persistence is considered to reflect both effectiveness and tolerability,[10] it does not capture important outcomes, especially the impact of these drugs on the prevention of structural damage. Despite the variability in the results of observational studies regarding b/tsDMARD persistence with or without concomitant use of csDMARD, most of the available evidence[22,26,27] and our results show that in patients with AS, the coadministration of a csDMARD in patients who initiate treatment with a b/tsDMARD is not indicated. In patients with PsA, evidence from other studies is highly inconsistent; however, the risk–benefit profile observed in our study suggests that until more robust evidence is available, b/tsDMARD monotherapy should be generally preferred in these patients. Finally, in patients with RA, due to the available evidence on the improved efficacy and reduced immunogenicity of the combination, the guidelines' recommendation in favour of adding a csDMARD to the b/tsDMARD should be followed, but our results support the importance of monitoring safety profile in this setting. Further long-term, pragmatic, randomized clinical trials that include the evaluation of radiographic progression, functionality, and other patient-reported outcomes would help to clarify the role of cotreatment with csDMARD when initiating b/tsDMARD therapy in patients with these clinical entities, especially in patients with PsA.

5 | CONCLUSIONS

Analysis of a large database collected under real-world conditions shows that initiation of targeted therapy in monotherapy has a significantly better persistence and safety profile than in combination with csDMARD in patients with PsA and AS. In patients with RA, the results also suggest that monotherapy should be considered as a therapeutic option with a higher chance of persistence.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Spanish Society of Rheumatology but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Spanish Society of Rheumatology.

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