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## Original Article

# Shaping rheumatoid arthritis treatment: Clinical and demographic drivers of tsDMARDs versus bDMARDs prescription post-EMA pronouncement on JAK inhibitors. Insights from the AMBI-RA study

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## ABSTRACT

**Objectives:** To evaluate the clinical-demographic drivers of treatment choice among targeted synthetic (ts-) and biologic (b-) disease-modifying anti-rheumatic drugs (DMARDs) and therapeutic outcomes in a cohort of patients with rheumatoid arthritis (RA) before and after the European Medicines Agency (EMA) pronouncement on Janus Kinase Inhibitors (JAKis) in January 2023.

**Methods:** This single-center, ambidirectional study enrolled patients with RA who were initiating a new course of b/tsDMARDs. Retrospective (2019–2022) and prospective cohorts (2023–2024) were compared, and disease activity and treatment response (achievement of remission or low disease activity) were evaluated at 3 and 6-month follow-up.

**Results:** The study analyzed 539 treatment courses (300 retrospective, 239 prospective) in 380 patients. Following the EMA guidelines, tumor necrosis factor- $\alpha$  inhibitors (TNFis) became the predominant bDMARD (from 32% to 41.4%), whilst JAKis prescriptions declined, particularly in the first-line settings (from 18% to 4.1%). The risk factors proposed by the EMA did not significantly prevent treatment with JAKis. However, we observed that a benefit associated with the first-line treatment in terms of target achievement (adjusted OR for non-response retrospective cohort 0.30, 95%CI 0.14–0.62) was mitigated in the prospective phase (OR 0.82, 95% CI 0.33–2.07).

**Conclusion:** The 2023 EMA pronouncement on JAKis led to a shift in prescription patterns, promoting TNFis versus JAKis. The decline in JAKis prescription did not appear to be driven by EMA-identified baseline risk factors, suggesting a generalized, categorical change. This channeling may have compromised the appropriateness of treatment choices, diminishing effectiveness in the prospective cohort, particularly for first-line therapies.

## 1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease leading to progressive joint damage and functional disability [1,2]. The treatment landscape for RA has evolved substantially over the last 30 years. Currently, a wide range of conventional synthetic (cs), biological (b), and targeted synthetic (ts) disease-modifying anti-rheumatic drugs

(DMARDs) have been licensed, leading to considerable improvements in clinical outcomes [3,4]. Among bDMARDs, five different tumor necrosis factor- $\alpha$  inhibitors (TNFis), one B cell-depleting agent (rituximab), two interleukin (IL)-6 receptor inhibitors (tocilizumab, sarilumab), and the T cell co-stimulation blocker (abatacept) are routinely adopted, while tsDMARDs approved for RA include the four Janus kinase inhibitors (JAKis) tofacitinib, baricitinib, upadacitinib, and filgotinib [5–7].

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According to the European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) recommendations for RA management, bDMARDs and tsDMARDs are recommended after csDMARDs failure, except for rituximab, which is approved after the failure of at least one previous bDMARD [8–10].

Recently, concerns regarding the safety profile of JAKis have emerged in randomized controlled trials (RCTs) of tofacitinib and baricitinib, regarding infections [11], malignancies, cardiovascular events (CVEs), and venous thromboembolic events (VTEs) [12]. These safety concerns prompted the U.S. Food and Drug Administration (FDA) to request an additional post-marketing clinical trial [13,14]. Specifically, in the ORAL Surveillance trial, the non-inferiority of JAKis versus TNFis concerning CVEs and malignancies risk in a CV-risk-enriched population was not demonstrated. Additionally, post-hoc analyses of the ORAL Surveillance trial found that, compared with TNFis, tofacitinib showed a potentially higher risk of major cardiovascular events (MACEs) and malignancies in specific high-risk populations [15,16]. In light of these findings, the European Medicines Agency (EMA) started a review procedure of the entire JAKis class safety, followed by a final pronouncement in January 2023, restricting all JAKis prescriptions only if no suitable alternatives are optionable in specific subgroups of patients, including patients over 65 years of age, current/former long-term smokers, and those with a high-risk profile in terms of cardiovascular or malignancies risk [17]. National Medicines Agencies then ratified these suggestions.

Although an increased risk has not been confirmed in several real-life studies [18–23], these limitations inevitably impacted prescriptions of tsDMARDs in real-life clinical practice, both in terms of new JAKis prescriptions as well as management of at-risk patients [24]. Nonetheless, the impact of EMA measures on JAKi prescribing attitudes has not been fully established, nor is it clear how such statements have influenced disease activity outcomes. To this end, several international recommendations [3,10] fail to provide specific suggestions to guide treatment prescriptions, describing only general guidance with no tailored focus on single patients' characteristics. Furthermore, the availability of biosimilars significantly impacts local and national prescription rules for DMARDs, further complicating prescription attitudes and the ability to draw firm conclusions [25].

The AMBI-RA study, focusing on the impact of the EMA alerts on clinical practice and investigating the strategy algorithms beyond drugs choice, aims to describe the clinical, laboratory, and instrumental factors associated with the clinician's choice of tsDMARDs rather than bDMARDs in a cohort of RA patients, before and after the EMA pronouncement on JAKis in January 2023. Furthermore, it aims to evaluate the patients' disease outcomes at 3- and 6-month follow-up.

## 2. Materials and methods

### 2.1. Ethics considerations

This study adhered to the ethical standards of the 1964 Declaration of Helsinki and its amendments. All procedures, including informed consent, complied with ICH Guidelines and U.S. CFR regulations (21 CFR Parts 50 and 56). The study protocol (CE-AVEC 493–2023-Oss-AOUFe) was approved by the IEC of the Area Vasta Emilia Centrale (AVEC), Italy (26/07/2023), and all the patients signed written informed consent.

### 2.2. Study design and setting

The AMBI-RA study is a single-center, ambidirectional cohort study, combining a retrospective and a prospective phase, assessing patients starting a new b/tsDMARD treatment course at the Rheumatology Unit, Department of Medical Sciences, University of Ferrara, and A.O.U. S. Anna, Ferrara, Emilia-Romagna. Treatment decisions were made based on international recommendations, guidelines, and local/regional

protocols (in the Emilia-Romagna region, from March 2022 onwards, a target of 75% TNFi-based first-line treatment was established [26]), independently of study inclusion [3,9]. All the clinical decisions regarding b/tsDMARDs start were taken after a collegial discussion in both cohorts, incorporating in the choice the patients' clinical characteristics, prior treatment history, and local prescribing constraints, in addition to regulatory guidance.

### 2.3. Participants

Patients were recruited from the RA outpatient clinic of the Rheumatology Unit, Ferrara Hospital. Treatment courses of patients diagnosed with RA (2010 ACR/EULAR criteria [27]), aged >18, and requiring new b/tsDMARD therapy were included. Retrospectively collected data refer to a retrospective phase including RA for which it was deemed necessary to start a first or new course of therapy with b/tsDMARDs in the period 01/01/2019–31/12/2022, and they are here referred as “retrospective cohort”, while prospectively collected data refer to a prospective phase including RA for which the initiation of a first or new course of therapy with b/tsDMARDs was deemed necessary after 01/01/2023, here referred as “prospective cohort”. Exclusion criteria included lack of informed consent, other chronic inflammatory arthritis, non-RA diagnosis, and positive pregnancy test at baseline.

### 2.4. Study procedures

In both cohorts, baseline demographic (age, gender, disease duration), lifestyle factors (smoking habits, alcohol use, physical activity, body mass index [BMI]), medical history and comorbidities (including fibromyalgia), current and previous RA treatments, including JAKis (baricitinib, filgotinib, tofacitinib, upadacitinib), TNFis (adalimumab, certolizumab, etanercept, golimumab, infliximab) and non-JAK/non-TNF inhibitors (abatacept, rituximab, sarilumab, tocilizumab), complete clinical evaluation and joints examination with tender and swollen joints counts (TJC and SJC), erythrocytes sedimentation rate (ESR) and C-reactive protein (CRP) measurements, disease activity scores (DAS28-CRP, Simplified Disease Activity Index [SDAI], Clinical Disease Activity Index [CDAI]), and physician global assessment (PhGA), patient-reported outcomes (Health Assessment Questionnaire–Disability Index [HAQ]; patient global activity [PtGA]; patient global pain visual analogic scale [Pt-Pain]; and Global Health [GH]) were collected. Comorbidities were measured using the Charlson Comorbidity Index (CCI) [28], excluding RA [29]. Follow-up visits were scheduled at 3 (T3) and 6 months (T6), according to the treat-to-target (T2T) strategy [30]. At each follow-up visit, a comprehensive clinical assessment was performed, including measurement of DAS28-CRP, SDAI, CDAI, PtGA, GH, Pt-pain, PhGA, HAQ, TJC, SJC, ESR, CRP, and review of current therapy. Adverse events (AEs) were collected and reported in the toxicity case report form, graded according to the corresponding CTCAE term (Version 5.0), and reported to the regulatory agencies. Data were recorded using a secure electronic data capture database for RA patients (<https://www.redcap.ospfe.it>) [31], hosted at the University Hospital of Ferrara.

### 2.5. Endpoints

The study's primary endpoint was the baseline treatment decision with bDMARDs or tsDMARDs. Secondary endpoints included achievement of remission (REM) or low disease activity (LDA) at T3–T6 (DAS28-CRP response criteria [32]), and non-response at T6 (defined as failure to achieve REM/LDA at T6 or b/tsDMARD discontinuation due to inefficacy before T6).

### 2.6. Statistical analysis

Therapeutic courses were considered as statistical units. Baseline

characteristics of the patients starting the various therapy courses were assessed through descriptive analyses and expressed as mean (standard deviation, SD) for continuous variables, and count and percentages for categorical variables. Univariable logistic regression was performed to assess factors associated with the choice of JAKis, TNFis, and non-JAK/non-TNF inhibitors, as well as with non-response at 6 months. Results were reported as odds ratios (ORs) with 95% confidence intervals (95% CI). Multivariable models were fitted with demographic and disease-related variables selected based on clinical significance and background knowledge (age, sex, disease duration, DAS28-CRP, smoking habits, CVD, oncological history, CCI, first-line b/tsDMARD, glucocorticoids (GCs) combination, MTX combination, csDMARD combination). All logistic regression models were fitted with robust standard errors, using a variance-covariance matrix adjusted for clustering by patients. P-values were adjusted for multiple testing with Holm correction. The modification of clinical and disease activity indices at T3 and T6 compared to baseline was assessed using the paired samples *t*-test or the Wilcoxon signed-rank test for normally and non-normally distributed variables, respectively. Interactions between b/tsDMARDs, disease duration, and first-line therapy were also evaluated. All analyses were performed separately for the retrospective and prospective cohorts. Regression analyses for treatment choice and non-response at six months were repeated, excluding patients treated with rituximab. In the sensitivity analysis, to take into account the role of the Emilia-Romagna regional policies of March 2022 promoting the use of TNFi biosimilars as first-line for the treatment of RA, we stratified the observation period into three time windows: (i) 2019–February 28, 2022; (ii) March 1, 2022–December 31, 2022; and (iii) January 1, 2023–November 20, 2024, and examined treatment patterns within each window. Moreover, both univariable and multivariable analyses were conducted to examine the association between b/tsDMARDs choice and clinical variables in a combined cohort, created by merging the retrospective and prospective cohorts. To evaluate the robustness in independent cohorts, we conducted a sensitivity analysis excluding patients who were present in both the retrospective and prospective cohorts. Specifically, we identified patients in the prospective cohort who had also been included in the retrospective cohort, and we excluded all therapeutic courses associated with these patients from the prospective cohort and re-ran the main analyses. All analyses were performed with Stata14 and R (4.4.2) [33].

### 3. Results

#### 3.1. Baseline demographic and clinical data

The study included 380 patients initiating 539 therapeutic courses: 300 in the retrospective (2019–2022) and 239 in the prospective cohort (2023–2024) (Tables 1–S1). The mean patient ages were 58.3 and 60.9 years, respectively, with disease durations of 11.4 and 14.5 years. CV disease was numerically more frequent in the prospective cohort (59% vs. 46.3%), with no remarkable difference in disease activity measures. Regarding treatment history, in the retrospective cohort, 42.7% of the treatment courses were started in b/tsDMARD-naïve patients, while 41.7% in TNFis-inadequate responders (IRs), 13.3% in JAKis-IR, and 30.3% in patients having failed at least one non-TNF/non-JAKis (mean number of prior b/tsDMARDs 1.1, SD 1.4). In the prospective phase, 30.5% of the treatment courses were in b/tsDMARDs naïve and 52.7% in TNFis-IR (mean number of prior b/tsDMARDs 1.7, SD 1.8). Despite the number of JAKis failures almost doubled in the prospective cohort with respect to the retrospective one (27.6 versus 13.3%), only a small proportion of patients in the prospective cohort (*N* = 11/58) had to stop the treatment with a recent JAKi due to concerns raised by the EMA recommendations (*N* = 3) or due to medical concerns related to comorbidities in general (*N* = 8), but not due to occurrence of cancer or CVD (Table S2).

**Table 1**

Baseline demographic and clinical characteristics of the sample.

| Patients' characteristics                             | Retrospective cohort ( <i>N</i> = 300) | Prospective cohort ( <i>N</i> = 239) |
|-------------------------------------------------------|----------------------------------------|--------------------------------------|
| <b>General characteristics</b>                        |                                        |                                      |
| Age (years), mean (SD)                                | 58.3 (±12.7)                           | 60.9 (±12.7)                         |
| Sex (F), <i>N</i> (%)                                 | 253 (84.3%)                            | 195 (81.6%)                          |
| Height (cm), mean (SD)                                | 164.6 (±10.3)                          | 165.2 (±9.1) /227                    |
| Weight (kg), mean (SD)                                | 67.9 (±16.5)                           | 71.3 (±19.4) /228                    |
| Caucasian, <i>N</i> /Obs (%)                          | 250/258 (96.9%)                        | 231/238 (97.1%)                      |
| Disease duration (years), mean (SD)                   | 11.4 (±9.3)                            | 14.5 (±11.2) /214                    |
| RF+, <i>N</i> /Obs (%)                                | 153/239 (64%)                          | 91/128 (71.1%)                       |
| ACPA+, <i>N</i> /Obs (%)                              | 139/235 (59.1%)                        | 79/122 (64.7%)                       |
| Actual Smokers, <i>N</i> /Obs (%)                     | 50/265 (18.9%)                         | 30/231 (13%)                         |
| Former smokers, <i>N</i> /Obs (%)                     | 71/265 (26.8%)                         | 70/231 (30.3%)                       |
| Never smokers, <i>N</i> /Obs (%)                      | 144/265 (54.3%)                        | 131/231 (56.7%)                      |
| <b>Disease activity</b>                               |                                        |                                      |
| CDAI, mean (SD)/Obs                                   | 21.5 (±6.7)/67                         | 22.4 (±9.4)/144                      |
| SDAI, mean (SD)/Obs                                   | 22.6 (±7.4)/66                         | 23.4 (±9.5)/138                      |
| DAS28-CRP, mean (SD)/ Obs                             | 4.3 (±0.9)/265                         | 4.2 (±1.1)/223                       |
| DAS28-ESR, mean (SD)/ Obs                             | 4.59 (1.12)/239                        | 4.65 (1.17)/206                      |
| ESR, mean (SD)/Obs                                    | 27.8 (±20.6)/264                       | 27.7 (±21.5)/216                     |
| CRP, mean (SD)/Obs                                    | 1.3 (±1.3)/293                         | 1.04 (±1.7)/234                      |
| TJC, mean (SD)/Obs                                    | 6.5 (±5.1)/291                         | 6.6 (±6.1)/235                       |
| SJC, mean (SD)/Obs                                    | 4.6 (±3.7)/291                         | 5.3 (±4.7)/235                       |
| TJC 28, mean (SD)/Obs                                 | 5.1 (±4.4)/291                         | 5.4 (±4.6)/235                       |
| SJC 28, mean (SD)/Obs                                 | 4.2 (±3.2)/291                         | 4.8 (±4.3)/235                       |
| PhGA, mean (SD)/Obs                                   | 60.2 (±15.1)/104                       | 56.9 (±16.6)/170                     |
| GH, mean (SD)/Obs                                     | 64.4 (±20.9)/276                       | 64 (±22.6)/220                       |
| PtGA, mean (SD)/Obs                                   | 64.5 (±22.3)/97                        | 65.9 (±22.4)/201                     |
| Patient global pain, mean (SD)/ Obs                   | 63.3 (±22.9)/228                       | 65.2 (±24.6)/215                     |
| HAQ, mean (SD)/ Obs                                   | 1.1 (±0.6)/170                         | 1.2 (±0.7)/120                       |
| <b>Comorbidities</b>                                  |                                        |                                      |
| CCI score, mean (SD)                                  | 0.5 (±0.8)                             | 0.5 (±0.8)                           |
| CCI = 0, <i>N</i> (%)                                 | 217/300 (72.3%)                        | 165/239 (69%)                        |
| CCI = 1, <i>N</i> (%)                                 | 35/300 (11.7%)                         | 34/239 (14.2%)                       |
| CCI > 1, <i>N</i> (%)                                 | 48/300 (16%)                           | 40/239 (16.7%)                       |
| Cardiovascular comorbidity (at least 1), <i>N</i> (%) | 139/300 (46.3%)                        | 141/239 (59%)                        |
| Neoplastic comorbidity (at least 1), <i>N</i> (%)     | 30/300 (10%)                           | 26/239 (10.9%)                       |
| <b>Baseline previous treatment</b>                    |                                        |                                      |
| b/ts-DMARD naïve, <i>N</i> (%)                        | 128/300 (42.7%)                        | 73/239 (30.5%)                       |
| TNFis failure, <i>N</i> (%)                           | 125/300 (41.7%)                        | 126/239 (52.7%)                      |
| JAKis failure, <i>N</i> (%)                           | 40/300 (13.3%)                         | 66/239 (27.6%)                       |
| Non-TNFis-non-JAKis failure, <i>N</i> (%)             | 91/300 (30.3%)                         | 95/239 (39.7%)                       |
| N° of previous b/tsDMARDs, mean (SD)                  | 1.1 (± 1.4)                            | 1.7 (± 1.8)                          |
| <b>b/tsDMARDs line</b>                                |                                        |                                      |
| 1st line                                              | 128 (43%)                              | 73 (31%)                             |
| 2nd line                                              | 83 (28%)                               | 66 (28%)                             |
| 3rd line or more                                      | 89 (30%)                               | 100 (42%)                            |
| <b>Concomitant treatment</b>                          |                                        |                                      |
| MTX treatment, <i>N</i> (%)                           | 169/300 (56.3%)                        | 115/239 (48.1%)                      |
| Concomitant csDMARD treatment, <i>N</i> (%)           | 199/300 (66.3%)                        | 141/239 (59%)                        |
| Concomitant GCs treatment, <i>N</i> (%)               | 190/300 (63.3%)                        | 118/239 (49.4%)                      |
| Concomitant NSAIDs treatment, <i>N</i> (%)            | 40/300 (13.3%)                         | 67/239 (28%)                         |

Abbreviations: SD, standard deviation; F, female; Obs, observations; RF, Rheumatoid Factor; ACPA, Anti-Citrullinated Protein Antibodies; CDAI, Clinical Disease Activity Index; SDAI, Simplified Disease Activity Index; DAS, Disease Activity Score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TJC, tender joint count; SJC, swollen joint count; TJC 28, 28-tender joint count; SJC 28, 28-swollen joint count; PhGA, Physician Global Assessment; GH, Global Health; HAQ, Health Assessment Questionnaire; CCI, Charlson Comorbidity Index; b/tsDMARDs, biologic/target synthetic Disease-Modifying Antirheumatic Agent; TNFis, TNF-inhibitors; JAKis, JAK-inhibitors; MTX, methotrexate; cs, conventional synthetic; GCs, glucocorticoids; NSAIDs, non-steroidal anti-inflammatory drugs.

### 3.2. Frequency of b/tsDMARD prescription

The most frequently prescribed DMARDs in the retrospective cohort were non-TNF/non-JAKis ( $N = 126$ , 42.7%), followed by TNFis ( $N = 96$ , 32%) and JAKis ( $N = 78$ , 26%). TNFis were mostly adopted in b/tsDMARD-naïve patients ( $N = 66$ , 51.6%), in combination with csDMARDs in 38.7% ( $N = 77$ ) courses. GCs were used as part of the combination therapy in 190 cases (63.3%). Regarding comorbidities, patients with CCI=0 received mostly a non-TNF/non-JAKis ( $N = 89$ , 41%) or a TNFi ( $N = 72$ , 33.2%). In those with CCI=1 and >1, TNFis were prescribed in 48.6% and 14.6% of cases, respectively, while JAKis were used in 11.4% and 37.5%. In the prospective cohort, TNFis were initiated in 41.4% of courses ( $N = 99$ ), JAKis in 16.3% ( $N = 39$ ), and non-TNF/non-JAKis in 42.3% ( $N = 101$ ). TNFis were the most prescribed drugs in b/tsDMARD-naïve patients (74%). Combination therapy with csDMARDs was used in 59% ( $N = 141$ ), and GCs in 49.4% ( $N = 118$ ). Interestingly, the decline among JAKi-based therapies was more pronounced for tofacitinib (from 39.7%,  $N = 31$ , to 5.1%,  $N = 2$ ) than for baricitinib (from 33.3%,  $N = 26$ , to 28.2%,  $N = 11$ ). Other JAKis, specifically upadacitinib (from 21.8%,  $N = 17$ , to 30.8%,  $N = 12$ ) and filgotinib (from 5.1%,  $N = 4$ , to 35.9%,  $N = 14$ ), saw an increase in their relative prescription rates. Additionally, the decrease in prescriptions for JAKis was mostly evident in the presence of CV or neoplastic comorbidities, advanced age, and smoking habits (Table 2).

### 3.3. Association between baseline clinical-demographic variables and b/tsDMARDs prescription in the retrospective cohort

In the retrospective cohort, JAKis were less prescribed as first-line treatments (OR 0.47, 95%CI 0.27–0.81,  $p = 0.007$ ) or in combination with any csDMARDs, including MTX (OR 0.30, 95%CI 0.16–0.55,  $p < 0.001$ ). Cancer history (OR 2.41, 95%CI 1.03–5.64,  $p = 0.42$ ) and longer disease duration (OR 1.04, 95%CI 1.01–1.07,  $p = 0.007$ ) were positively associated with JAKis' use instead, but no association remained significant in the multivariate analysis after correction. For TNFis, first-line use (OR 5.04, 95%CI 2.94–8.64,  $p < 0.001$ ), csDMARDs combination (OR 2.72, 95%CI 1.50–4.93,  $p = 0.001$ ) and current smoking (OR 2.13, 95%CI 1.13–3.99,  $p = 0.019$ ) were positive associations, while advanced age (OR 0.98, 95%CI 0.97–1,  $p = 0.036$ ), cancer history (OR 0.34, 95%CI 0.11–0.78,  $p = 0.013$ ), comorbidities (CCI>1, OR 0.34, 95%CI 0.16–0.76,  $p = 0.008$ ), GCs use (OR 0.47, 95%CI 0.28–0.77,  $p = 0.003$ ), and disease duration (OR 0.96, 95%CI 0.93–0.99,  $p = 0.004$ ), were negative. Multivariable regression analysis confirmed that first-line use was the only significant positive association (OR 4.35, 95%CI 2.14–8.87,  $p < 0.001$ ,  $q = 0.001$ ). Non-TNF/non-JAKis were less likely prescribed as first-line treatments (OR 0.43, 95%CI 0.26–0.70,  $p = 0.001$ ), but positively associated with MTX co-administration (OR 1.76, 95%CI 1.10–2.81,  $p = 0.019$ ), GCs use (OR 2.10, 95%CI 1.28–3.45,  $p = 0.003$ ), and cardiovascular disease (OR 1.70, 95%CI 1.05–2.77,  $p = 0.032$ ) in the univariate regression analysis. After correction, however, no association remained significant in the multivariate analysis (Table S3, Fig. 1). Results were consistent in direction, magnitude, and statistical significance after the exclusion of rituximab courses in sensitivity analyses (full data available in Table S4).

### 3.4. Association between baseline clinical-demographic variables and b/tsDMARDs prescription in the prospective cohort

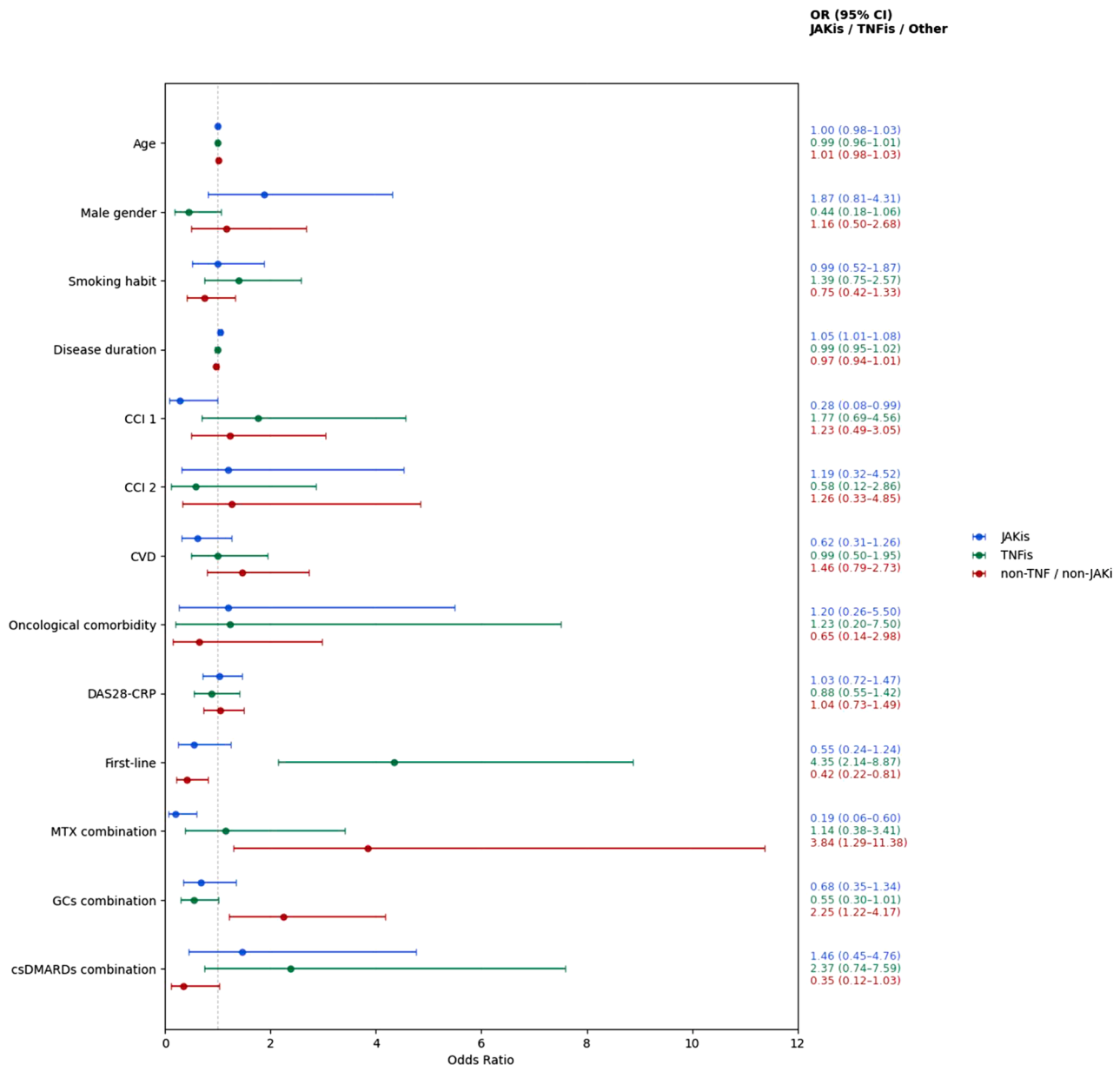
In the prospective cohort, JAKis were less frequently prescribed as first-line therapy (OR 0.15, 95%CI 0.05–0.52,  $p = 0.003$ ), with MTX (OR 0.31, 95%CI 0.15–0.67,  $p = 0.003$ ) or other csDMARDs (OR 0.28, 95%CI 0.14–0.58,  $p = 0.001$ ), and in older patients (OR 0.97, 95%CI 0.95–0.99,  $p = 0.008$ ), whereas they were more likely to be prescribed in patients with higher DAS28-CRP scores (OR 1.53, 95%CI 1.06–2.21,  $p = 0.0259$ ), and longer disease duration (OR 1.03, 95%CI 1–1.05,  $p = 0.048$ ). Multivariable analysis confirmed the negative association with age and

**Table 2**

Frequency of b/tsDMARDs' prescription according to patients' characteristics.

| b/tsDMARD                                         | Retrospective cohort<br>( $N = 300$ ) | Prospective cohort<br>( $N = 239$ ) |
|---------------------------------------------------|---------------------------------------|-------------------------------------|
| TNFis, n/N (%)                                    | 96/300 (32%)                          | 99/239 (41.4%)                      |
| Etanercept                                        | 61/96 (65.5%)                         | 58/99 (58.6%)                       |
| Adalimumab                                        | 29/96 (30.2%)                         | 32/99 (32.3%)                       |
| Certolizumab                                      | 6/96 (6.2%)                           | 5/99 (5%)                           |
| Golimumab                                         | 0/96 (0%)                             | 3/99 (3%)                           |
| Infliximab                                        | 0/96 (0%)                             | 1/99 (1%)                           |
| <b>Non-TNF/non-JAKis, n/N (%)</b>                 | 126/300 (42.7%)                       | 101/239 (42.3%)                     |
| Tocilizumab                                       | 20/126 (15.9%)                        | 44/101 (43.6%)                      |
| Sarilumab                                         | 33/126 (26.2%)                        | 5/101 (4.9%)                        |
| Abatacept                                         | 50/126 (39.7%)                        | 31/101 (30.7%)                      |
| Rituximab                                         | 23/126 (18.2%)                        | 21/101 (20.8%)                      |
| <b>JAKis, n/N (%)</b>                             | 78/300 (26%)                          | 39/239 (16.3%)                      |
| Tofacitinib                                       | 31/78 (39.7%)                         | 2/39 (5.1%)                         |
| Baricitinib                                       | 26/78 (33.3%)                         | 11/39 (28.2%)                       |
| Upadacitinib                                      | 17/78 (21.8%)                         | 12/39 (30.8%)                       |
| Filgotinib                                        | 4/78 (5.1%)                           | 14/39 (35.9%)                       |
| <b>First line treatment, n/N (%)</b>              | 128/300 (42.7%)                       | 73/239 (30.5%)                      |
| TNFis                                             | 66/128 (51.6%)                        | 54/73 (74%)                         |
| JAKis                                             | 23/128 (18%)                          | 3/73 (4.1%)                         |
| Non-TNF/non-JAKis                                 | 39/128 (30.5%)                        | 16/73 (21.9%)                       |
| <b>csDMARD combination, n/N (%)</b>               | 199/300 (66.3%)                       | 141/239 (59%)                       |
| TNFis                                             | 77/199 (38.7%)                        | 66/141 (46.8%)                      |
| JAKis                                             | 37/199 (18.6%)                        | 13/141 (9.2%)                       |
| Non-TNF/non-JAKis                                 | 85/199 (42.7%)                        | 62/141 (44%)                        |
| <b>Methotrexate combination, n/N (%)</b>          | 169/300 (56.3%)                       | 115/239 (48.1%)                     |
| TNFis                                             | 61/169 (36.1%)                        | 51/115 (44.3%)                      |
| JAKis                                             | 27/169 (16%)                          | 10/115 (8.7%)                       |
| Non-TNF/non-JAKis                                 | 81/169 (47.9%)                        | 54/115 (47%)                        |
| <b>Glucocorticoid combination, n/N (%)</b>        | 190/300 (63.3%)                       | 118/239 (49.4%)                     |
| TNFis                                             | 49/190 (25.8%)                        | 47/118 (39.8%)                      |
| JAKis                                             | 49/190 (25.8%)                        | 20/118 (16.9%)                      |
| Non-TNF/non-JAKis                                 | 92/190 (48.4%)                        | 51/118 (43.2%)                      |
| <b>CCI* = 0, n/N (%)</b>                          | 217/300 (72.3%)                       | 165/239 (69%)                       |
| TNFis                                             | 72/217 (33.2%)                        | 76/165 (46%)                        |
| JAKis                                             | 56/217 (25.8%)                        | 32/165 (19.4%)                      |
| Non-TNF/non-JAKis                                 | 89/217 (41%)                          | 57/165 (34.5%)                      |
| <b>CCI* = 1, n/N (%)</b>                          | 35/300 (11.7%)                        | 34/238 (14.2%)                      |
| TNFis                                             | 17/35 (48.6%)                         | 11/34 (32.3%)                       |
| JAKis                                             | 4/35 (11.4%)                          | 2/34 (5.9%)                         |
| Non-TNF/non-JAKis                                 | 14/35 (40%)                           | 21/34 (61.8%)                       |
| <b>CCI* &gt; 1, n/N (%)</b>                       | 48/300 (16%)                          | 40/238 (16.7%)                      |
| TNFis                                             | 7/48 (14.6%)                          | 12/40 (30%)                         |
| JAKis                                             | 18/48 (37.5%)                         | 5/40 (12.5%)                        |
| Non-TNF/non-JAKis                                 | 23/48 (47.9%)                         | 23/40 (57.5%)                       |
| <b>Cardiovascular comorbidity, n/N (%)</b>        | 139/300 (46.3%)                       | 141/239 (59%)                       |
| TNFis                                             | 41/139 (29.5%)                        | 52/141 (37%)                        |
| JAKis                                             | 30/139 (21.6%)                        | 24/141 (17%)                        |
| Non-TNF/non-JAKis                                 | 68/139 (48.9%)                        | 65/141 (46.1%)                      |
| <b>Oncological history, n/N (%)</b>               | 30/300 (10%)                          | 26/239 (10.9%)                      |
| TNFis                                             | 4/30 (13.3%)                          | 6/26 (23.1%)                        |
| JAKis                                             | 13/30 (43.3%)                         | 2/26 (7.7%)                         |
| Non-TNF/non-JAKis                                 | 13/30 (43.3%)                         | 18/26 (69.2%)                       |
| <b>Advanced age (&gt;65 y. o.), n/N (%)</b>       | 111/300 (37%)                         | 101/239 (42.2%)                     |
| TNFis                                             | 28/111 (25.2%)                        | 38/101 (37.6%)                      |
| JAKis                                             | 31/111 (27.9%)                        | 5/101 (4.9%)                        |
| Non-TNF/non-JAKis                                 | 52/111 (46.8%)                        | 58/101 (57.4%)                      |
| <b>Current smokers, n/N (%)</b>                   | 50/265 (18.9%)                        | 30/231 (13%)                        |
| TNFis                                             | 22/50 (44%)                           | 14/30 (46.7%)                       |
| JAKis                                             | 10/50 (20%)                           | 4/30 (13.3%)                        |
| Non-TNF/non-JAKis                                 | 18/50 (36%)                           | 12/30 (40%)                         |
| <b>Smoking history (current or past), n/N (%)</b> | 121/265 (45.7%)                       | 100/231 (43.3%)                     |
| TNFis                                             | 38/121 (31.4%)                        | 40/100 (40%)                        |
| JAKis                                             | 35/121 (28.9%)                        | 12/100 (12%)                        |
| Non-TNF/non-JAKis                                 | 48/121 (39.7%)                        | 48/100 (48%)                        |

\* CCI was calculated excluding RA. Abbreviations: b/tsDMARDs, biologic/target synthetic Disease-Modifying Antirheumatic Agent; TNFis, TNF-inhibitors; JAKis, JAK-inhibitors; CCI, Charlson Comorbidity Index.



**Fig. 1.** Forest plot showing the association between clinical and demographic characteristics and b/tsDMARD choice in the multivariable analysis (retrospective cohort).

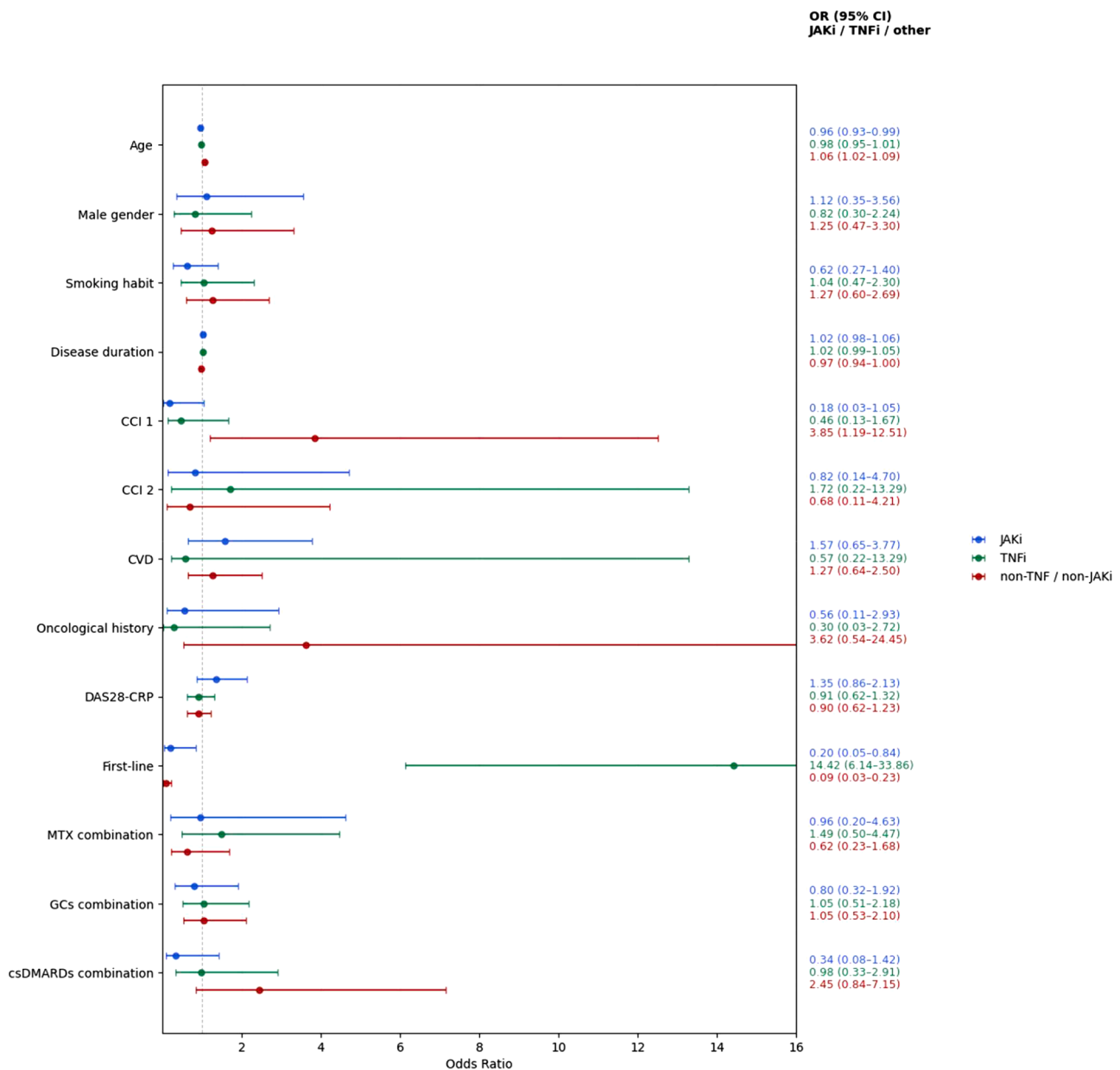
Abbreviations: CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; DAS28-CRP, Disease Activity Score 28 joints C-reactive protein; b/tsDMARD, biologic/target synthetic disease-modifying antirheumatic drug; MTX, methotrexate; GCs, glucocorticoids; csDMARDs, conventional synthetic disease-modifying antirheumatic drug; JAKi, JAK inhibitors; TNFi, TNF inhibitors.

first-line treatment, but statistical significance was lost after adjustment. TNFis were strongly associated with first-line treatment (OR 7.64, 95% CI 4.07–14.34,  $p < 0.001$ ) and negatively with age (OR 0.97, 95% CI 0.95–0.99,  $p = 0.010$ ) and cancer history (OR 0.39, 95% CI 0.15–1.02,  $p = 0.055$ ), the latter with borderline significance. Multivariable analysis confirmed the strong link with first-line b/tsDMARD use (OR 14.4, 95% CI 6.14–33.86,  $p < 0.001$ ), even after adjustment ( $q < 0.001$ ). Non-TNF/non-JAKis, instead, were less used as first-line treatment (OR 0.27, 95% CI 0.14–0.51,  $p < 0.001$ ), but more common in older patients (OR 1.06, 95% CI 1.03–1.08,  $p < 0.001$ ), those with higher CCI (OR 3.06, 95% CI 1.41–6.64,  $p = 0.005$  for CCI=1; OR 2.56, 95% CI 1.23–5.34,  $p = 0.012$  for CCI >1), and cancer history (OR 3.52, 95% CI 1.50–8.27,  $p = 0.004$ ). After multivariable analysis and correction, only age (OR 1.06, 95% CI 1.02–1.09,  $p = 0.001$ ,  $q = 0.014$ ) and first-line use (OR 0.09, 95% CI 0.03–0.23,  $p < 0.001$ ,  $q < 0.001$ ) remained significant (Table S5; Fig. 2),

even after rituximab exclusion in a dedicated sensitivity analysis (full data in Table S6).

### 3.5. Association between baseline clinical-demographic variables and b/tsDMARDs prescription according to relevant timeframes

We additionally stratified treatment courses into three timeframes: (i) 2019–February 28, 2022; (ii) March 1, 2022–December 31, 2022; and (iii) January 1, 2023–November 20, 2024, anchored to the March 2022 Emilia-Romagna regional guidance on the use of TNFis as first-line [26], and the subsequent EMA regulatory recommendations on JAK inhibitors [17]. The March–December 2022 sub-cohort included only 65 treatment courses (30 TNFi, 12 JAKi, and 23 non-TNFi/non-JAKi) and, notably, no first-line JAKi initiations. However, the drug-class distribution in March–December 2022 was closer to that observed in the prospective



**Fig. 2.** Forest plot showing the association between clinical and demographic characteristics and b/tsDMARD choice in the multivariable analysis (prospective cohort).

Abbreviations: CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; DAS28-CRP, Disease Activity Score 28 joints C-reactive protein; b/tsDMARD, biologic/target synthetic disease-modifying antirheumatic drug; MTX, methotrexate; GCs, glucocorticoids; csDMARDs, conventional synthetic disease-modifying antirheumatic drug; JAKi, JAK inhibitors; TNFi, TNF inhibitors.

cohort (Tables S7-S10). In the combined cohort analyses (2019–2024), JAKis use declined significantly in 2023 (OR 0.21, 95%CI 0.08–0.56,  $p = 0.002$ ,  $q = 0.037$ ), while TNFi prescriptions rose since 2022, with 2023 remaining significant after correction (OR 5.92, 95%CI 2.48–14.8,  $p < 0.001$ ,  $q = 0.002$ ). JAKis' prescriptions were associated with longer disease duration but negatively with CCI=1, csDMARD/MTX use, and first line, with the latter being statistically significant even after correction (OR 0.38, 95%CI 0.20–0.70,  $p = 0.002$ ,  $q = 0.037$ ). TNFis were positively associated with first-line use (OR 7.89, 95%CI 4.74–13.5,  $p < 0.001$ ,  $q < 0.001$ ), csDMARDs, and smoking, but negatively with age and GC use. Non-TNFi/non-JAKis were linked to older age, comorbidities, and cancer history, but were less often used as first-line (OR 0.25, 95%CI 0.15–0.40,  $p < 0.001$ ,  $q < 0.001$ ) (Tables S11-S13).

### 3.6. Analysis in independent cohorts

To address the potential carry-over of treatment history across periods inherent to a course-based design (which could add confounding by refractory disease and prior treatment failures that could influence post-EMA prescribing independently of the EMA recommendations), we performed a sensitivity analysis excluding patients contributing to both the retrospective and prospective cohorts (46 overlapping patients; 62 treatment courses removed from the prospective cohort) and repeated all analyses. Results showed that the multivariable associations remained statistically significant, except for older age, which was no longer significantly associated with the initiation of non-TNFi/non-JAKi therapies (Table S14-S16).

### 3.7. Disease activity at 3 and 6 months of follow-up

Follow-up was available for 229 out of 300 courses at T3 and 237 out of 300 at T6 in the retrospective cohort, with 99 non-responders at T6 (41.8%), and 26 out of 90 non-responders among first-line courses (29%). At T3, REM was reached in 98/229 courses (42.8%, 95%CI 36.3–49.5) and LDA in 140/229 courses (61.1%, 95%CI 54.5–67.4). At T6, REM was reached in 45.1% of courses (107/237, 95%CI 38.7–51.7) and LDA in 58.6% (139/237, 95%CI 52.1–64.9) (Table S17).

In the prospective cohort, follow-up information was available for 184 and 154 of 239 therapeutic courses at 3 and 6 months, respectively. At T6, 78/154 (50.6%) were non-responders in the whole cohort, and 17/45 (38%) were non-responders among first-line courses. Disease activity at T3 reached the state of REM in 57/184 (31.0%, 95%CI 24.5–38.3), and LDA in 97/184 (52.7%, 95%CI 45.3–60.1). At T6, REM was reached in 33.1% of courses (51/154, 95%CI 25.9–41.2) and LDA in 49.3% (76/154, 95%CI 41.3–57.5) (Table S17). Additionally, disease activity scores and patient outcomes improved significantly over time in both cohorts (Table S18).

Furthermore, we conducted a stratified analysis of remission and low disease activity (LDA) rates at 6 months post-treatment initiation, categorizing patients by line of treatment (first-line, second line, and subsequent to third line). Overall, target attainment was generally lower in the prospective cohort than in the retrospective cohort, particularly in first-line treatments and most notably at T6, in which remission decreased from 58.9% (retrospective cohort) to 42.2% (prospective cohort) (Table S17, Fig. 3).

### 3.8. Associations between clinical-demographic factors and non-response

First-line treatment was the only factor negatively associated with

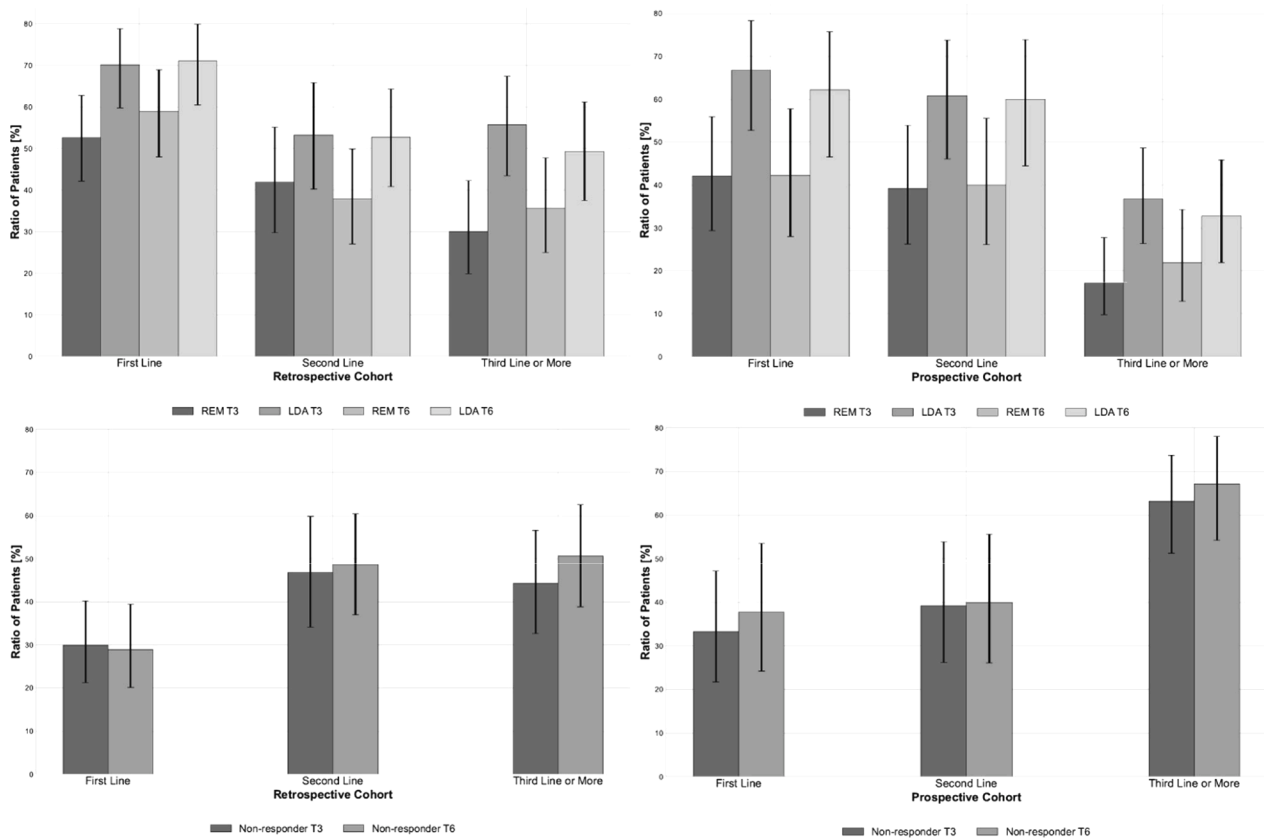
non-response at 6 months in the retrospective cohort (OR 0.30, 95%CI 0.14–0.62,  $p = 0.013$ ), even after adjustment ( $q = 0.013$ ) and exclusion of rituximab (Tables S19–S20, Fig. 4). Other factors associated with non-response at the univariate analysis included increased comorbidity burden ( $CCI > 1$ , OR 2.79, 95%CI 1.30–5.98,  $p = 0.009$ ), cancer history (OR 2.97, 95%CI 1.25–7.05,  $p = 0.014$ ), and higher disease activity (OR 1.89, 95%CI 1.30–2.74,  $p = 0.001$ ).

Conversely, in the prospective cohort, first-line treatment was not significantly associated with non-response (OR 0.82, 95%CI 0.33–2.07,  $p = 1$ ,  $q = 1$ ), while elevated DAS28-PCR (OR 2.15, 95%CI 1.46–3.17,  $p < 0.001$ ) and GCs use (OR 1.98, 95%CI 1.06–3.7,  $p = 0.033$ ) were associated with non-response at univariate regression analysis (Tables S21–S22, Fig. 4). In the analysis excluding rituximab, MTX (OR 0.47, 95%CI 0.24–0.93,  $p = 0.031$ ) and other csDMARDs (OR 0.43, 95%CI 0.21–0.88,  $p = 0.021$ ) were negatively associated with non-response in univariate but not in multivariate analyses (Table S23).

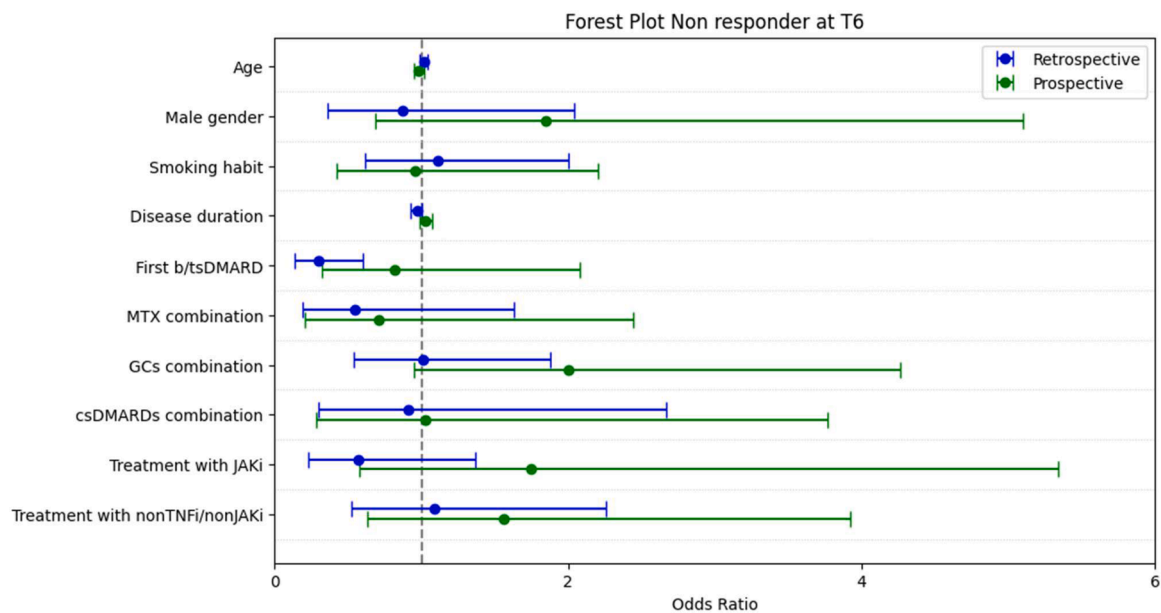
## 4. Discussion

The AMBI-RA is a single-center observational cohort study analyzing treatment courses with b/tsDMARDs before and after the EMA guidance on JAKis, and, to the best of our knowledge, the first study with an ambidirectional design to assess the impact of the EMA recommendations on clinical outcomes in RA [17]. The most relevant finding of this study was that a reduction in JAKis courses was largely driven by a categorical restriction of the prescriptions rather than by a risk-stratified prescribing approach, resulting in worse outcomes.

Our results show that TNFis became the predominant b/tsDMARD (from 32% to 41.4% of all treatments and from 51.6% to 74% as first-line agents), mainly driven by the availability of biosimilars and the influence of regulatory measures, not only from the EMA but also from



**Fig. 3.** A: Comparison between the percentage of treatment courses reaching REM and LDA at T3 and T6 in the retrospective and prospective cohorts. B: Comparison between the percentage of non-responders at T6 in the retrospective and prospective cohorts, divided according to treatment lines. Abbreviations: REM, remission; LDA, low disease activity; T3, third month of follow-up; T6, sixth month of follow-up; pts, patients.



**Fig. 4.** Forest plot assessing the association between clinical and demographic characteristics and non-response in the multivariable analysis.

Abbreviations: b/tsDMARD, biologic/target synthetic disease-modifying antirheumatic drug; MTX, methotrexate; GCs, glucocorticoids; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; JAKi, JAK inhibitors; TNFi, TNF inhibitors.

regional policies (in Emilia-Romagna Region, Italy, a target of 75% TNFi-based first-line treatment was set starting from March 2022 [26]). Concomitantly, JAKis prescriptions declined significantly, particularly in the first-line settings (from 18% to 4.1%), indicating a broad retreat from JAKis. Non-TNF/non-JAKis prescriptions remained stable overall, but their use was more common in older patients or subsequent lines of therapy [34]. Interestingly, although the study design precludes causal inference, we found that the prescription of JAKis after the publication of the EMA recommendations does not appear to be influenced by the risk factors identified by the EMA. Indeed, neither advanced age, smoking, cardiovascular comorbidities, nor cancer history influenced the decision to initiate or avoid a JAKi-based treatment. Overall, this suggests that the post-EMA decline in JAKis use reflected a broad shift in prescribing practice rather than an individualized, risk-stratified implementation of the guidance. Consequently, JAKis prescribing appeared to decrease in response to heightened safety concerns in general (as well as local prescription policies), rather than being preferentially curtailed in patients with higher baseline CV or neoplastic risk as EMA intended. And this was further demonstrated in sensitivity analyses considering the relevant timeframes. Despite the limited numbers and the absence of first-line JAKis prescriptions in the cohort March-December 2022, which formally precluded the adoption of multivariable models, the distribution of prescribed drug classes was more similar to that observed in the prospective cohort than in the retrospective cohort, with the decline of JAKis becoming significant only after 2023.

Other studies have documented a reduction in JAKis utilization after the publication of the ORAL Surveillance trial and the subsequent EMA recommendations. The English National Health Service (NHS) documented a slowdown in the prescription of tofacitinib due to concerns regarding VTE, followed by a further decline after the association with risk of MACEs, and an even more pronounced decrease after the extension of safety warnings to the entire class of JAKis. Similar trends were observed for baricitinib, while prescriptions for upadacitinib and filgotinib increased despite the EMA restrictions [35]. The initiation of a first-line treatment with a JAKi was also less common in Germany after the EMA recommendations, with courses based on JAKis generally reserved for patients who have already failed multiple treatment lines [36]. Comparable findings were observed in the U.S., where JAKis'

prescriptions (particularly tofacitinib and baricitinib) declined following the release of preliminary ORAL Surveillance data, accompanied by an increase in TNFis use [37]. A relative increase in the use of more selective JAKis was also reported in a recent Italian study, which showed a decline in tofacitinib and baricitinib prescriptions alongside a rise in upadacitinib use [38]. These trends may reflect a perceived more favorable risk/benefit profile of the more selective JAK1 inhibitors, such as upadacitinib and filgotinib, among prescribers, with the JAK-pot study providing real-world evidence for the safety of JAKis in terms of adverse events, which were similar for JAKis versus TNFis but lower for TNFis compared to tofacitinib, suggesting a drug-specific rather than a class-wide effect [39–41].

Our study was divided into a retrospective and a prospective observation period. Previous studies have mostly investigated retrospectively the characteristics of patients receiving JAKis before and after the safety data and EMA recommendations, often resulting in different and conflicting results. In France, the baseline characteristics of patients receiving JAKis treatment before and after the EMA VTE warning showed a trend towards a lower proportion of patients with a history of VTE after May 2019 [42]. Data from the German RABBIT registry showed that patients receiving JAKis before the safety warnings were more likely to have CVD, VTE, or oncologic risk factors [43]. Similar results coming from the U.S. Veterans Affairs Health System indicate a tendency for reduced JAKis treatment initiation and increased JAKis discontinuation among older patients and cardiovascular comorbidities, with decreased age and cardiovascular comorbidities in patients initiating tofacitinib after January 2021, but no significant decrease in the proportion of patients with a history of cancer or VTE [44]. In contrast, a sensitivity analysis performed on courses based on JAKis before and after the ORAL Study publication among commercially insured patients with RA did not demonstrate any meaningful difference in terms of baseline risk factors among patients using JAKis or TNFis [45]. Even if our study was not intended to evaluate the decision to continue or to swap treatment in patients already receiving JAKis after the EMA recommendations, data from real-world cohorts show that a substantial proportion of patients classified as “high-risk” under EMA criteria continued to receive JAKis, particularly in difficult-to-treat (D2T) RA populations with few therapeutic alternatives [46,47]. Notably, more than half of JAKi users in Italy [24] and 80% in the UK [48] would not

meet EMA eligibility criteria, yet many had previously failed multiple bDMARDs, and JAKis showed favorable drug survival in this subgroup [49–53]. An Italian cohort study showed that only a small proportion of patients requested JAKis discontinuation due to concerns about the EMA recommendation [54]. Indeed, since the risk factors proposed by the EMA are common in the general population (and enriched in a population with inflammatory diseases like RA [23,55–57]), an indiscriminate application of these stringent rules would exclude many patients from JAKis therapy; hence, the final decision to initiate treatment rests with the physician, who should weigh the risk factors against the potential benefits of such treatment.

Examining the impact of the EMA recommendation on the clinical outcomes of our patients, we observed a decrease in the proportion of treatment courses reaching REM and LDA at T3 and T6 in the prospective compared to the retrospective cohort. Specifically, the percentage of courses reaching REM at T3 decreased from 42.8% to 31% and from 45.1% to 33.1% at T6, while the percentage of courses reaching LDA at T3 decreased from 61.1% to 52.7% and from 58.6% to 49.3% at T6 (Fig. 3). Moreover, the percentage of non-responders at T6 increased from 41.8% to 50.6%. These findings suggest that achieving remission was less likely in the prospective cohort compared to the retrospective one. Additionally, although a negative association between first-line treatment and non-response at 6 months was observed in the retrospective cohort, this association was not observed in the prospective cohort. This finding aligns with an overall reduction in therapeutic target attainment in the prospective cohort, particularly among first-line treatments, and most notably at T6. These results may reflect the impact of EMA safety recommendations, which appear to have led to a shift in patient treatment from JAKis (and non-TNF/non-JAKis) to TNFi-based therapies. Consequently, the appropriateness of treatment choices, particularly though not exclusively, in the context of first-line therapy, may have been compromised. At the same time, given that the prospective cohort had a higher number of b/tsDMARD-experienced patients (69.5% vs. 57.3%), we acknowledge that it may include a higher proportion of difficult-to-treat cases, which could have influenced the clinical efficacy of treatment decisions. However, given that up to 40% of patients do not respond to initial treatment with TNFis in settings in which clinical decisions are not influenced by the EMA recommendations [58], it is reasonable to assume that the issuance of these recommendations (along with the observed increase in TNFis prescriptions at the expense of JAKis use) might have contributed to a higher proportion of treatment courses failing to respond to initial therapy.

Our study has several limitations, including its single-center design and limited external generalizability. For this reason, our findings should be viewed as hypothesis-generating rather than definitive. In this context, single-center studies play an important exploratory role, particularly when regulatory changes act as “natural experiments” that are difficult to evaluate within randomized or highly standardized frameworks [24]. These findings should not be interpreted as a direct causal effect of regulatory restrictions, but rather as an association that warrants further investigation in larger, multicenter populations. Moreover, single-center cohorts allow for a high degree of clinical, organizational, and policy homogeneity, reducing variability related to differences in prescribing cultures, access to therapies, reimbursement rules, and local implementation of regulatory guidance [59–61]. This internal consistency is particularly relevant when the research question focuses on the consequences of regulatory and policy-driven constraints rather than on estimating population-wide prescription rates. In the context of the Emilia-Romagna Healthcare system, regional prescribing targets and reimbursement rules are clearly defined and systematically applied, providing a well-characterized framework in which regulatory recommendations act as a natural experiment. Importantly, these constraints are not unique to this region, as similar cost-containment measures, biosimilar-driven policies, and hierarchical treatment algorithms are increasingly adopted across other Italian regions and European healthcare systems [24,51,62]. Therefore, while the absolute

prescription proportions observed in our cohort may not be directly generalizable, the mechanisms underlying prescribing shifts are likely relevant beyond the local setting. Moreover, single-center studies have played a key role in the early evaluation of changes in JAKis utilization and safety following the ORAL Surveillance trial and subsequent regulatory actions, often preceding and informing larger registry-based analyses [24,54]. Such studies are particularly suited to capturing nuanced clinical decision-making, including deviations from intended risk-stratified approaches, that may be diluted or obscured in large administrative datasets. In this sense, single-center data remain a necessary exploratory step to generate hypotheses and identify clinically meaningful signals that warrant confirmation in broader, multicenter, and international cohorts.

Another limitation of our study is the choice of a specific date to delineate the retrospective and prospective phases. Although discussions about JAK inhibitor safety emerged earlier, following the ORAL Surveillance trial (January 2022) and PRAC/EMA opinions (October 2022) [14,63], a clearly defined cut-off was required for a reproducible study design. After careful discussion within the study steering committee, we selected 01/01/2023 as the boundary, reflecting the period immediately preceding the operationalization of EMA indications in Italian clinical practice and before formal acknowledgment by AIFA in March 2023 [64]. This pragmatic choice allowed us to minimize misclassification of treatment courses that could have been influenced by early safety signals while maintaining a clear distinction between pre- and post-guidance prescribing patterns.

We acknowledge that rheumatologists may have been influenced by preliminary safety signals before the formal EMA pronouncement [38]. While our study cannot fully disentangle the effect of early warnings from the formal guidance, we performed sensitivity analyses according to relevant timeframes, and we demonstrated that the chosen cut-off provides a reproducible framework for examining the downstream consequences of regulatory measures on prescribing behavior and clinical outcomes.

We adopted the DAS28-CRP definition for REM/LDA as the outcome, instead of other measures such as the ACR/EULAR definition of remission [65], which allowed us to assess the outcome in a relatively larger number of therapeutic courses, at least for the retrospective phase, in which CDAI and SDAI were recorded for only a minority of courses. The short-term follow-up period (6 months) aligns with the need to establish the effectiveness of the treatment decisions in the context of the T2T approach [30]. Finally, the AEs assessment was outside the scope of this study, and this could be explored in future analyses with longer follow-up. Notwithstanding these limitations, the strengths of the AMBI-RA study lie in its ambidirectional design, the robust number of treatment courses, and the well-balanced prospective and retrospective cohorts, together enabling a real-world comparison before and after a key regulatory shift, with a focused evaluation of how EMA safety recommendations may have influenced target attainment.

In conclusion, our study demonstrated that EMA safety warnings, in addition to local regulatory guidance, have influenced prescription attitudes of b/tsDMARDs in RA patients of the Emilia-Romagna region, favoring TNFis over JAKis. Notably, the decline in JAKis use did not appear to be selectively driven by EMA-identified baseline risk factors in our cohort, suggesting a broad change in prescribing behavior, rather than a risk-stratified implementation. Taken together, these findings indicate that regulatory and policy measures may have acted synergistically to favor TNFis-based strategies and amplify concerns toward JAKis therapy. This therapeutic shift may have reduced the flexibility of clinicians in b/tsDMARDs choice, impacting clinical effectiveness, particularly for first-line users. Future research should investigate the long-term impact of this treatment shift in terms of efficacy and safety outcomes. A more personalized and balanced approach that weighs both safety and disease control should be better defined to improve the outcomes for RA patients.

## Ethics statement

This study was approved by the AVEC Review Board, and it was performed following the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The review of this protocol by the IRB/IEC and the performance of all aspects of the study, including the methods used for obtaining informed consent, were also carried out following the principles enunciated in the declaration, as well as the ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Patients, and Part 56 Institutional Review Boards. The IEC of the Area Vasta Emilia Centrale (AVEC) approved the study protocol (approval code: CE-AVEC 493–2023-Oss-AOUFe). All the patients enrolled signed the informed consent. The patients provided their written informed consent to participate in this study.

## Author contributions

All the authors meet the following criteria: (i) acquisition, analysis, or interpretation of data for the work; (ii) drafting the work or revising it critically for important intellectual content; (iii) provide approval for publication of the content; (iv) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Declaration of competing interest

Ettore Silvagni has received research support from AbbVie and Lilly and consulting/speaker's fees from AbbVie, Alfa-Sigma, Lilly, UCB, and Novartis. Beatrice Maranini has received research support for attending meetings from Novartis and UCB, as well as speaker's fees from Novartis. Marcello Govoni has received research support for attending meetings from AbbVie, Eli Lilly, Alfasigma, and GSK, as well as consulting/speaker's fees from AbbVie, Alfasigma, Lilly, UCB, AstraZeneca, and GSK. The other authors declare no conflicts of interest.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version, at [doi:10.1016/j.ejim.2026.106852](https://doi.org/10.1016/j.ejim.2026.106852).

## Data availability

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be sent to the corresponding author.

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