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Trajectories of Adherence to Biologics in Patients with Rheumatoid Arthritis and Risk of a Secondary Immuno-Mediated Inflammatory Disease: A Large Multi-Database Italian Study

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BACKGROUND

Rheumatoid arthritis (RA) is an immune-mediated inflammatory disease (IMID) with a global prevalence of approximately 1%. The therapeutic strategy, aiming at achieving low disease activity, includes both conventional and biologic disease-modifying anti-rheumatic drugs (bDMARDs). Evidence from the literature suggests that patients with one IMID are at higher risk of developing another. However, data are lacking on the association between the occurrence of secondary IMIDs and longitudinal adherence to bDMARDs.

AIM

To evaluate the association between adherence trajectories to bDMARDs and the occurrence of secondary IMIDs in patients with RA.

METHODS

We conducted a population-based retrospective observational cohort study using administrative data [1]. We included residents of the participating regions from 2010 to 2023 who had at least one biologic dispensing approved for RA, and a diagnosis of RA identified though a validated algorithm. We excluded individuals younger than 18 years, had less than one year of continuous enrolment (look-back), were prevalent users of RA bDMARDs, were treated with rituximab as index drug, or had a diagnosis of any IMID other than RA during the look-back period. The first dispensing date of a bDMARD was defined as the index date. Patients were observed over a two-year period: the first year (exposure period) to assess adherence, and the second year (follow-up period) to monitor the occurrence of secondary IMIDs, death, or end of the study period—whichever came first. During the exposure period, patients were censored if they developed cancer, became pregnant, or died. Treatment coverage was estimated assuming a daily intake of one Defined Daily Dose. We assessed adherence to bDMARDS monthly over the exposure period using the Medication Possession Ratio. Adherence trajectories were identified using Group-Based Trajectory Modeling (GBTM) [2,3]. We used a Cox proportional hazards model to estimate the hazard ratio, and corresponding 95% confidence interval, for developing a secondary IMIDs.

RESULTS

We identified a cohort of 35,600 individuals, with a higher proportion of females (78%), and a mean age of 56.5 (standard deviation: 14.0). We identified four distinct adherence trajectories over a 12-month period. Group 3, labeled as the High Adherent group and comprising 49.7% of participants, maintains nearly 100% adherence consistently throughout the entire follow-up period, indicating stable and optimal adherence. Group 1, referred to as the Declining Adherent group and accounting for 11.0% of the sample, starts with high adherence but shows a gradual and marked de-

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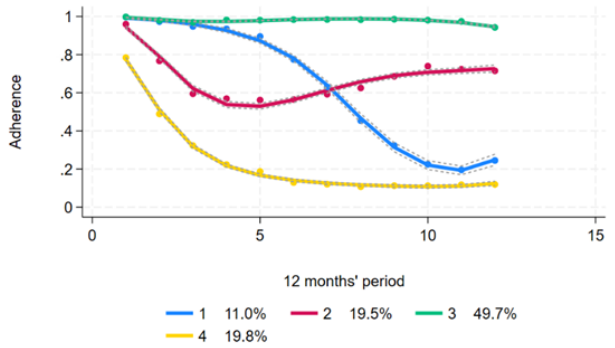
cline, particularly after the fifth month, reaching levels around 0.2 by month 12. Group 2, named the Moderate Adherent group and comprising 19.5% of the sample, experiences an initial drop in adherence in the early months, followed by an increase and stabilization around 0.6 to 0.7. Group 4, described as the Low Adherent group and representing 19.8% of participants, demonstrates a steep and continuous decline in adherence from the beginning, falling below 0.2 within the first few months and remaining low for the rest of the follow-up period, highlighting significant variability in adherence behaviors across the groups.

During the one-year of follow-up, 205 events of secondary IMIDs were observed. The Cox proportional hazards model did not reveal statistically significant differences in the risk of developing a secondary IMID across the adherence trajectory groups (overall p = 0.20). Compared to the High Adherent group (Group 3, reference), the Declining Adherent group (Group 1) had a hazard ratio (HR) of 1.28 (95% CI: 0.83–1.99), the Moderate Adherent group (Group 2) had an HR of 0.67 (95% CI: 0.43–1.04), and the Low Adherent group (Group 4) showed a non-significant increase in risk with an HR of 1.11 (95% CI: 0.78–1.59).



CONCLUSION

The study identified four distinct trajectories of bDMARD adherence, showing marked heterogeneity in patients' behaviors. However, there were no statistically significant differences in the risk of developing a second IMID between the groups. These findings suggest that factors other than adherence may influence the occurrence of autoimmune comorbidities.

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