Change Over Time in the Pattern of Clinical Response to First-line Biologic Drugs in Patients with Rheumatoid Arthritis: Observational Data in a Real-life Setting

To the Editor:

In the last 2 decades, the management of rheumatoid arthritis (RA) was dramatically changed by the introduction of the treat-to-target (T2T) approach[1,2,3] and biologic disease-modifying antirheumatic drugs (bDMARD). The effectiveness of those targeted therapies to achieve remission and low disease activity (LDA) has been demonstrated in randomized controlled trials[4], progressively increasing the use of bDMARD as a real-life application of the T2T strategy. Nevertheless, in the main international registries, the baseline median disease duration of bDMARD starters has been reported to be significantly high, possibly affecting the overall clinical response to this drug class[5,6].

To evaluate the real effect of T2T recommendations on RA management with bDMARD, we retrospectively analyzed the baseline characteristics and the 1-year clinical response in a cohort of patients with RA who received a first-line bDMARD in our Rheumatology Unit from September 1999 to December 2015, stratifying the study population according to the period of enrollment (1999–2004, 2005–2009, and 2010–2015) and disease duration (under vs over 2 yrs), and analyzing data according to an intent-to-treat protocol. Eligible study population was extracted from a local registry approved by the Gaetano Pini Institute Ethics Committee (approval no. 150_2002), including all patients who signed the informed consent for any subsequent retrospective analysis of clinical data. All analyzed clinical information is reported as anonymous aggregate data, excluding any identifiable medical information. Intergroup differences were analyzed by the chi-square test for dichotomous variables and Kruskal-Wallis test for continuous variables. One-year clinical response was defined as the proportion of patients achieving Disease Activity Score at 28 joints (DAS28) remission (< 2.6) or LDA (≥ 2.6 and < 3.2)[7].

The analysis included 725 patients [82.9% women, mean age (± SD) 53.9 yrs (± 12.5), median disease duration (interquartile range) 8.48 yrs (4.34–15.72)] treated with tumor necrosis factor inhibitors (n = 648), anakinra (n = 15), abatacept (n = 29), tocilizumab (n = 27), or rituximab (n = 6). As reported in Table 1, we observed a significant decrease over time of baseline median disease duration, mean Health Assessment Questionnaire-Disability Index score, and mean DAS28.

Moreover, we found a gradually increased proportion of patients [from 22.9% (1999–2004) to 37.8% (2010–2015), p = 0.0002] beginning bDMARD in moderate disease activity (DAS28 ≥ 3.2 and < 5.1), with a concomitant decrease over time [from 75.5% (1999–2004) to 58.2% (2010–2015), p < 0.0001] of bDMARD starters in high disease activity (DAS28 > 5.1). In addition, we observed a progressively increasing number of patients with earlier RA (≤ 2 yrs) receiving the first bDMARD (6.9%, 9.8%, and 14.1% for 1999–2004, 2005–2009, and 2010–2015 subgroups, respectively). Those data showed the gradual change of biologic-treated population baseline characteristics toward the inclusion of patients with early RA, less disability, and a lower disease activity, demonstrating a better rheumatologists' adherence to T2T strategy. As remarked by Aga, *et al* in a Norwegian Disease Modifying Antirheumatic Drug Registry cohort analysis, during the last decade clinicians have implemented modern, more aggressive treatment strategies, which will lead to better longterm disease outcomes[8].

In our study population, 24.8% and 11.2% of patients achieved 1-year remission or LDA, respectively. After stratification by calendar period of enrollment, the 1-year remission rate was significantly higher (p < 0.0001) in 2010–2015 (35.9%) and 2005–2009 (30.2%) subgroups compared with the 1999–2004 subgroup (11.7%), whereas no difference emerged in comparison of 1-year LDA rate in the 3 evaluated periods (13.6%, 9.8%, and 10.6%, respectively; p = 0.41). The OR for achieving 1-year remission was significantly higher in early (≤ 2 yrs; n = 79) compared with late (> 2 yrs; n = 646) patients with RA (41.8% vs 22.7%, respectively; OR 2.435, 95% CI 1.501–3.950, p = 0.0005), whereas no differences were observed in 1-year LDA between the same subgroups (10.1% vs 11.3%, respectively; OR 0.8844, 95% CI 0.4092–1.911, p = 0.8519).

Our 16-year, real-life clinical experience clearly demonstrates the increasing tendency of an earlier bDMARD introduction in the disease course, even in patients with moderate disease activity and less severity. Moreover, in the most recently analyzed period (2010–2015), about 50% of our patients achieved remission/LDA, despite an overall baseline median disease duration of more than 6 years. Even if our study has not been designed and powered for analyzing the rigorousness in the application of the T2T strategy, the described trend may be considered as a reasonable consequence of a better adherence to the European League Against Rheumatism T2T recommendations.

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Table 1. Baseline characteristics of study population.

Characteristics	1999–2004, n = 274	2005–2009, n = 245	2010–2015, n = 206	p
Age, yrs, mean (SD)	54.49 (12.66)	53.34 (12.17)	53.94 (12.73)	0.5629*
Disease duration, yrs, median (IQR)	10.37 (5.51–17.09)	7.51 (3.79–15.51)	6.64 (3.38–15.03)	0.0003*
Female, %	87.6	81.6	78.2	0.0202**
DAS28, mean (SD)	5.788 (1.154)	5.352 (1.158)	5.146 (1.333)	< 0.0001*
HAQ-DI, median (IQR)	1.75 (1.375–2.125)	1.5 (1–1.875)	1.125 (0.875–1.625)	< 0.0001*
Methotrexate use, %	71.2	62	59.2	0.0003**
Patients in moderate disease activity, %	22.9	37.5	37.8	0.0002**
Patients in high disease activity, %	75.5	60	58.2	< 0.0001**

* Kruskal-Wallis test. ** Chi-square test. IQR: interquartile range; DAS28: Disease Activity Score at 28 joints; HAQ-DI: Health Assessment Questionnaire–Disability Index.

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