Treatment in rheumatoid arthritis and mortality risk in clinical practice: the role of biologic agents

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Abstract

Objective

To assess the mortality rate (MR) and the mortality risk of a rheumatoid arthritis (RA) inception cohort, with and without biologic agents (BAs). Other factors associated to mortality were also investigated.

Methods

Retrospective longitudinal study of RA patients, attending the rheumatology outpatient clinic of a tertiary Hospital (Madrid), collected over 5 years (2000–2004), and followed from the diagnosis of RA up to the patients' death, lost to follow-up or September 2013. The dependent variable was death and the independent variable was exposure to BAs. Covariables: sociodemographic, clinical and therapy variables. MR was expressed per 1,000 patient-years with the 95% confidence interval [CI]. BA influence on MR was analysed by multivariable Cox models. Clinical and therapy variables were used in a time-dependent manner. The results are expressed in hazard ratio (HR) and [CI].

Results

We included 576 patients and 711 courses of therapy. 19.6% were taking BA, 86% disease-modifying anti-rheumatic drugs (DMARDs) (70% on methotrexate - MTX), and 12% were untreated. There were 133 deaths during 4,981.64 patient-years at risk. The MR for BA was 12.6 [6–26], for DMARDs was 22.3 [18.4–27.1], and for those without treatment was 89.1 [61.9–128.2]. The adjusted HR for mortality in those exposed to BA versus those not exposed was 0.75 [0.32–1.71]). Other variables independently associated with mortality were: age, rheumatoid factor, hospital admissions, Health Assessment Questionnaire (HAQ), and MTX use (HR: 0.44 [0.29–0.66]).

Conclusion

BAs and standard DMARDs are more effective in decreasing mortality compared to no therapy. Patients exposed to BAs were not associated with a significant increase or decrease in mortality when compared to patients with non-biological DMARDs. The use of MTX remains the only drug that has independently shown a beneficial effect on mortality.

Key words

rheumatoid arthritis, mortality, biologic agents

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Introduction

It seems that mortality remains higher in patients with rheumatoid arthritis (RA) compared to general population (1, 2). The reasons behind this are multifactorial and may include the effects of chronic persistent inflammation, disability, and comorbidity (3-5). It seems that disease-modifying anti-rheumatic drugs (DMARDs) may decrease the risk of premature mortality. In fact, previous studies have suggested that the control of inflammation with methotrexate (MTX) may decrease the mortality risk (6).

During the last decades, treatment strategies in RA have changed, through early intensive treatment with full dose of DMARDs in combination, and also the emergence of biologic agents (BAs). Nowadays, the main goal of treatment in RA patients is to prevent joint damage and disability, achieving "remission", or at least a state of low disease activity (7). In fact, it seems that course of disease activity and functional disability in patients with RA has become milder over the past several years (8).

Focusing on BAs, these drugs have been shown to improve the clinical symptoms and the disability course of RA (9-11). Whether or not these treatments can also improve the mortality rate in RA remains unknown. Seven observational studies and one meta-analysis have investigated the impact of TNF-α inhibitors or rituximab on mortality, with conflicting results. Four of them suggested a reduced mortality risk compared to those not treated with BAs (12-15), whereas the other four did not (16-19). Nevertheless we have to take into account that the follow-up length, design, type of patients, disease duration, the type of analysis and confounders are different among studies. However, to analyse long-term outcomes such as mortality, the impact of changes in exposure, concomitant therapy and in the risk profiles of the patients over time should be considered (13, 14).

Our main objective was to evaluate the mortality risk in a cohort of RA patients treated with TNF-α inhibitors, rituximab, tozilimumab or abatacept, compared with patients without these drugs (without DMARDs, MTX alone or in combination with other DMARDs). We also aimed to estimate the impact of the different sociodemographic, clinical and therapy factors on mortality.

Methods

Study design

We carried out a retrospective observational study using an inception cohort of RA patients from January 2000 to December 2004 and followed up to 14 years after diagnosis, (December 2013). Patient data were obtained during routine clinical practice, following the usual procedure for observational studies in our centre, with the oral informed consent of patients to be treated in a service that has clinical assistance and research work. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices, and was approved by the institutional ethics committee (CEIC Hospital Clínico San Carlos – Madrid).

Patients

We selected all the patients who fulfilled the 1987 American College of Rheumatology classification criteria for RA, attending the rheumatology outpatient clinic of the Hospital Clínico San Carlos (Madrid, Spain).

The investigators retrospectively reviewed all the medical records to obtain the variables. For the period between 2000 and December 2006, they were on paper and after that period, data were recorded in a departmental electronic health record (MEDI <log>) used in our outpatient clinic.

Variables

The primary outcome was all-cause mortality, and it was obtained from the National Death Index of Spain (INDEF data base from the Ministry of Health). Biologic agents administered, including etanercept, golimumab, certolizumab, infliximab, adalimumab, rituximab, abatacept, or tozilizumab, were used as independent variables.

The following covariates were included: a) sociodemographic baseline characteristics: such as gender, age, marital status; b) clinical characteristics: baseline cardiovascular disease and comorbidities

Table I. Baseline demographic and clinical characteristics of patients (n=576).

Characteristics	
Age at diagnosis, mean ± SD	59.8 ± 16
Women	74
Married, %	51
Cardiovascular disease, %	20.2
HAQ, mean ± SD	0.7±0.6
DAS 28, mean ± SD	3.8±1.26
Rheumatoid factor positive, %	60
Biologic agents, n (%)	113 (19.6)
DMARDs, n (%)	480 (86)
Glucocorticoids, %	67
Hospital admissions, %	
None	66
1	16
2	8
3	6
≥4	5

that were defined as the number of hospital admissions during the follow-up, and were assessed using the hospital discharge register;

c) disease related variables during the study period: rheumatoid factor maximum value (RF), and disease activity/severity: measured by the average Disease Activity Score of 28 joints (DAS-28) during the first year;

d) the functional status measured by mean HAQ during the first year;

e) other drugs also prescribed: concomitant glucocorticoids (yes or not, and mean dosage during the first three months); and number of concomitant DMARDs (including MTX and other DMARDs [leflunomide, antimalarials, gold salts, cyclosporine, azatiprine or sulfasalazine]).

At baseline and at different time points of follow-up (depending on whether the patient was treated with biological agents or not) we assessed in each patient the functional and clinical status, concomitant therapy prescribed, and comorbidity (14).

Statistical analysis

Continuous variables were described using mean and standard deviation or median and interquartile rank. Categorical variables were described with proportions. Survival techniques were used to estimate the mortality rate (MR) in our cohort, expressed per 1,000 patient-years with their respective 95% confidence interval (CI). Kaplan-Meier curves were set to account for deaths over time. Time of exposure for the patients with RA comprised the period from the baseline visit (diagnosis visit) until the occurrence of any of the following cut-off points: lost to follow-up, death for any cause or the end of the study (December 2013). It is important to note that real life conditions use complicated patterns of drug therapies. Thus, patients were included in different groups and contributed with patient-years at risk to both those exposed and those not exposed to BAs treatment.

Cox bivariate analyses were made to assess differences in mortality. Cox multivariate regression models (adjusted for age, sex, disability, comorbidity, disease severity and all variables with a *p*-value less than 0.15 in the bivariate analysis) were run to examine the possible influence of BAs/MTX/other DMARDs/no therapy on mortality rate. Biological Agents were used in a time-dependent manner. Health Assessment Questionnaire (HAQ), DAS-28, concomitant glucocorticoids, DMARDs, and comorbidities were also used in a time-dependent manner. Results were expressed by hazard ratio (HR) and with the 95% Confidence Interval [CI]. Proportional hazard assumption was tested using Schoenfeld residuals and the scaled Schoenfeld residuals. All analyses were performed using Stata v. 12 statistical software (Stata Corp., College Station, TX, USA). A two-tailed *p*-value under 0.05 was considered to indicate statistical significance.

Results

Between January 2000 and December 2004, 576 RA patients A were included in the inception cohort, with a total follow up of 4,981.6 patient-years. 58% of the patients ended the study, whereas 42% did not: 19% were lost to follow-up and 23% died during the study period. Table 1 shows the baseline characteristics of the study group: Most of them were women in their sixties. At baseline, they had moderate level of disease activity, and slight levels of disability. Glucocorticoids were used in 67% of the patients with a median average dose of 6.5 (5–10) mg. More than 50% of the patients had comorbid conditions during the study period that required hospitalisation, with the most common conditions being Infections (mainly pneumonia), cancer, congestive heart failure and ischaemic heart disease.

From the beginning of the study, 86% of the patients were treated with at least one DMARD (range 1–6), MTX being the most frequent (70%). Only one patient started with BA. During the follow-up 19.6% of the patients

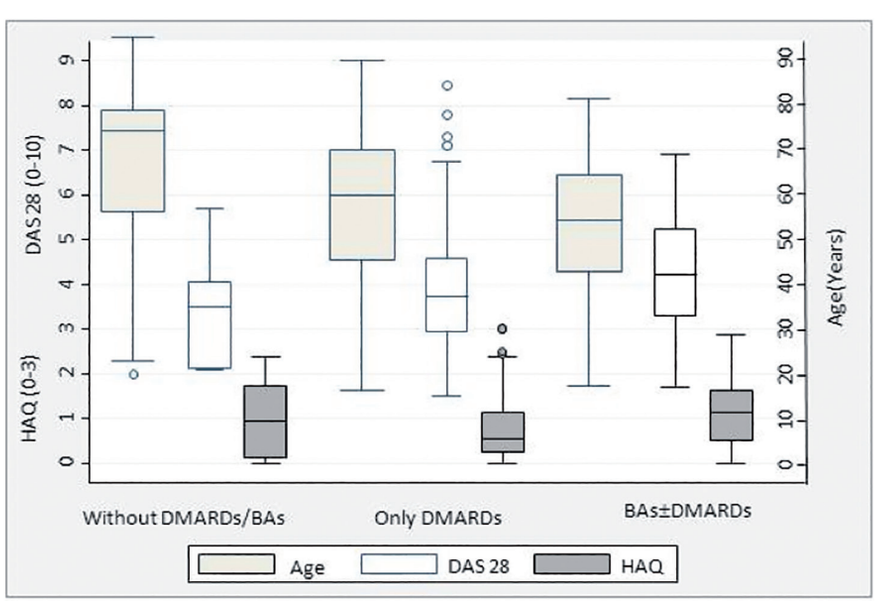

Fig. 1. Description of sociodemographic and disease characteristics of the patients by different types of therapy regimens.

used biologic agents (median 2, range 1–6 per patient), all except 7 patients were taking concomitant DMARDs. The median lag time from diagnosis to BA onset was 4.3 (2.1–6.5) years. Sociodemographic and disease characteristic of the patients differed in relation to the type of therapy used (Fig. 1). At baseline, patients without any treatment were older and with less disease activity than those with DMARDs and those with BA (median [p25–75] age in years: 73.8 [56–78], 60.9 [46–71], 54.3 [42.8–64.6], $p<0.0001$; median DAS–28 [p25–75]: 3.5 [2.1–4.0], 3.7 [2.9–4.6], 4.2 [3.3–5.24], $p<0.04$).

During follow up, 133 patients died with a crude mortality rate estimated in 24 subjects per 1,000 patient-years [95% CI: 19.6–27.68]. As we see in Figure 2, 5%, 10%, 25% and 30% of the patients had died within three, five, ten and 12 years of diagnosis respectively. The mortality rate as expected was higher in males and in older people. In relation to therapy, using DMARDs and specifically MTX or BAs had less mortality rate. In fact, there were 12 deaths per 1,000 patient-years among those treated with BAs compared with 28.4 deaths per 1,000 patient-years among those not treated (Table II; Fig. 2).

Table III displays the bivariate analysis. Regarding sociodemographic characteristics of the patient, the age achieved statistical significance. Basal cardiovascular disease and a higher number of hospital admissions during the different periods clearly influenced in death. In disease related variables, patients with high rheumatoid factor and higher HAQ had more unadjusted hazard to die. Regarding concomitant therapy, glucocorticoids increased the risk, whereas taking DMARDs, specifically MTX decreased the risk. Concerning BAs, patients taking these medications had 69% less probability to die compared to those not treated.

Cox multivariate regression analysis was done to adjust for variables that were unevenly distributed between patients taking and not taking BAs and that had an association with the outcome. The final model is shown in Table IV including sociodemographic, clinical and disease related variables. We found that survival in patients receiving BAs was not different to those not receiving BAs, (adjusted HR: 0.75 [95% CI: 0.3–1.7]). Nevertheless, using MTX was associated with lower mortality risk, with 2.32 times less probability compared to those patients not using MTX. We found a trend of less mortality and the number of DMARDs during the study period ($p=0.1$), but without statistical significance. The mean dose of glucocorticoids (HR: 1.12 [0.85–1.5], $p=0.383$) in the first three months of each period of therapy did not reached statistical significance and dropped from this model. Age, high rheumatoid factor, hospital admissions and high disability during the study period, were found to be predictors of mortality as expected.

Interestingly, we had 12% of patients without BAs neither DMARDs, thus we analysed therapy as the use or not of

Table II. Mortality rate (IR) by gender, age, and treatment regimens during follow-up.

	n	Events (n)	IR per 100	95% CI
Gender				
Female	3,689.5	90	24.4	19.8-29.9
Male	1,292.14	43	33.3	24.6-44.8
Age at diagnosis (years)				
<45	1,171.3	0	-	-
45-59	1,310.8	13	9.9	5.7-17.1
60-74	1,775.2	54	30.4	23.3-39.7
≥75	7,24.1	66	91.1	71.6-116.1
DMARDs				
with	4,656.2	104	22.3	18.4-27.1
without	325.44	29	89.1	61.9-128.2
MTX				
with	3,674.8	53	14.4	11-18.8
without	1,306.84	67	56.4	44.4-71.6
BA				
with	552.2	7	12.6	6-26.5
without	4,429.44	126	28.4	23.8-33.8

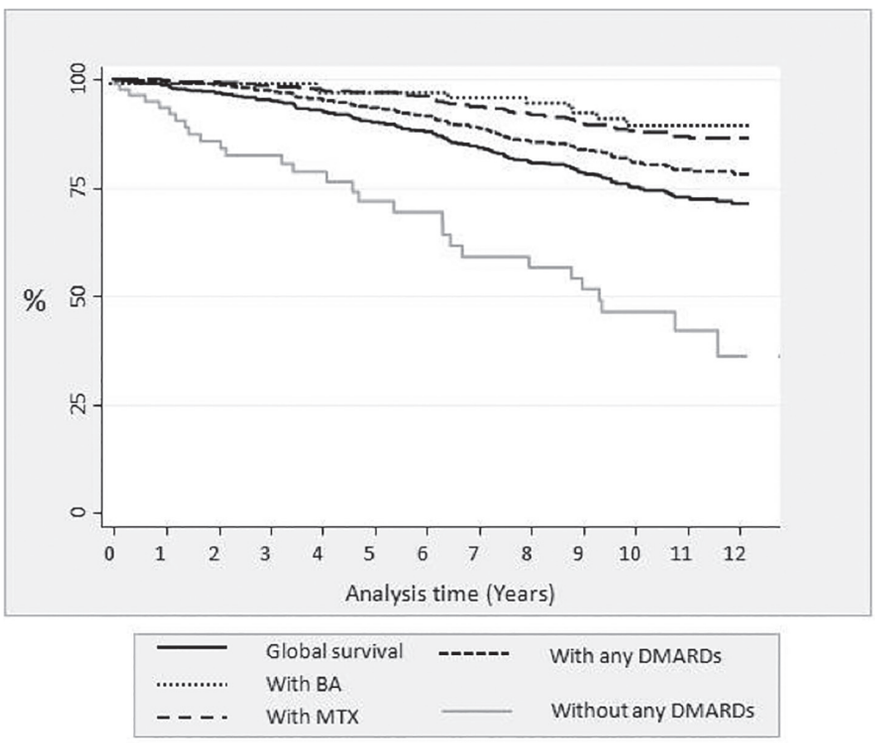

Fig. 2. Kaplan-Meier survival estimate. Global and by different type of therapy regimens.

Table III. Effect of the biologic agents and other variables on death. Bivariate analysis.

	Bivariate analysis		
	HR	CI 95%	*p*
Male gender	1.38	0.96-2.0	0.08
Age at diagnosis	1.10	1.08-1.12	0.000
Married	1.23	0.89-1.71	0.2
Rheumatoid factor	1.32	0.9-1.92	0.1
Basal cardiovascular disease	4.08	2.0-8.3	0.000
Hospital admissions	1.21	1.14-1.28	0.000
DAS 28 (>5.1)	1.66	0.8-3.4	0.1
HAQ (>1.5)	1.65	0.9-2.9	0.009
Biologic agents	0.59	0.39-0.90	0.014
MTX	0.25	0.17-0.36	0.000
Other DMARDs	0.59	0.48-0.74	0.000
Corticoids	1.04	1.01-1.08	0.009

Table IV. Effect of the biologic agents on death. Multivariate analysis.

	Multivariate analysis		
	HR	CI 95%	*p*
Male gender	1.02	0.68-1.53	0.8
Age at diagnosis	1.09	1.07-1.12	0.000
Positive rheumatoid factor	2.01	1.4-2.98	0.000
Biologic agents	0.75	0.32-1.71	0.4
MTX	0.44	0.29-0.66	0.000
Other DMARDs	0.73	0.48-1.1	0.1
DAS 28 (>5.1)	1.58	0.75-3.35	0.2
HAQ (>1.5)	2.0	1.09-3.6	0.025
Hospital admissions	1.19	1.13-1.26	0.000

any disease-modifying treatment. We could see after adjusting with all the variables of the final previous model and concomitant glucocorticoids, that "using DMARDs and/or BAs" decreased the hazard of mortality (HR: 0.52 [0.32–0.86]; p=0.001) compared to using no therapy. Moreover if we categorised this variable into "no therapy" (reference category), "DMRADs or BAs" (HR: 0.51 [0.31–0.85]; p=0.01), "DMARDs and BAs" (HR: 0.39 [0.15–0.99]; p=0.04) the statistical differences appeared in all categories. We did not perform a separate category as "using only BA", due to the small number of cases we had. We also compared the categories "DMARDs and BAs" *vs*. "DMARDs or BAs", without statistical differences (HR: 0.68 [0.29–1.5]; p=0.3). Interestingly, glucocorticoids did not achieve statistical significance in none of the models.

Proportionality of the models was tested using the Schoenfeld and the scaled Schoenfeld residuals. All global model p-values were >0.3. We assumed that the models did not violate the proportional assumption.

Discussion

We have evaluated the association between DMARDs, BA therapy, and mortality in rheumatoid arthritis patients. We have assessed that BAs and standard DMARDs are more effective decreasing mortality compared to no therapy. We have also shown that, patients exposed to biologic agents were not associated with a significant increase or decrease in mortality when compared to patients with non-biological DMARDs. Moreover, we have corroborated the role of several variables on mortality.

The cohort included is representative of the RA population in Spain (20), most of them women in their sixties. Moreover, our study also provides a wide real range of patients with a large variety of therapeutic possibilities in the management of RA in clinical practice as in other similar settings (21). 88% of the patients were taking DMARDs and 19% of them in combination with BAs. As expected, patients on BA were younger and with more disease activity. It is notable that 12% of our patients did not receive any type of classical or biological DMARDs, but management in real life is sometimes complex enough to implement the best therapeutic option (22, 23). In general, the main reasons described in our cohort for patients without therapy were old age, incompatibility related to concomitant comorbidities-medications, presence of many adverse drug reactions, poor adherence to the treatment and/or patient preferences.

The mortality rate shown in our study is close to most of the other published studies (1, 2, 17). The meta-analysis of Dadoun *et al*. (1), including publications until 2010 showed that the mean mortality rate between studies was 27 [23-34] per 1,000 patient-years. More recent studies (13, 16) also incorporated the mortality rate according to the therapy used. In the study of Lunt *et al*. (16) the mortality rate for BAs was 16.8 [15.8–18] and for non-BAs was 21.6 [18.8–24.8] per 1,000 patient-years. Maybe our mortality rate observed on BAs was somewhat lower, but we have to take into account than we have analysed an inception cohort, not established RA patients.

The main results of the present study are broadly similar to those from a British cohort and from the study of Herrinton performed in USA, which observed no association of anti-TNF-α therapy with mortality compared to non-biologic DMARD, when controlling with baseline confounders (16,17).

Other studies conducted in Sweden (14) Spain (12) and Germany (13) reported a reduced mortality among RA patients with established disease treated with anti-TNF-α agents and rituximab compared with conventional DMARD therapy. In the first two studies, national registries of anti-TNF-α users were compared with geographically narrower cohorts of non-users. The Swedish study (14) included adjustment for a wide variety of disease-related features, including disease activity, disability and therapy, in a time dependent manner similar to our analysis. But comorbidity was limited to baseline chronic obstructive pulmonary disease, diabetes, and cardiovascular disease. The covariable DMARDs was defined as previously used without specification among types,

neither MTX. Regarding the Spanish study, it was limited to a small sample size and it was adjusted for baseline age, DAS-28, disease duration and gender by propensity score. Finally, the study of Listing *et al*. (13), included the registry RABBIT with a large sample size, long follow-up and considered changes in the activity of RA, in functional capacity, fluctuating dosages of glucocorticoids, and in the treatment with synthetic or biologic DMARDs over time. Nevertheless, their results can be just applicable to the population analysed, that is different from ours (an inception cohort with a wide real variety of non-selected patients seen in the outpatient setting). In RABBIT, patients with established RA who do well on methotrexate monotherapy were not included, thus this register included patients with high disease severity despite MTX. Therefore, this study might have generated an underestimation of the beneficial effect of MTX (6).

In fact, in our study we have confirmed the protective effect on death of MTX regardless other therapies used (5, 6). We also found that other conventional DMARDs did not have a significant effect on mortality, also shown in the observational study of Choi *et al*. (6).

Using time-dependent proportional hazards model in our cohort, helps to corroborate the role of other different exposure variables on mortality. Disability reflected by a high HAQ, was found to be a strong predictor of mortality as in many other previous studies (3, 26-30), although we have defined disability as an average HAQ in each period. Comorbidity, translated by the number of hospital admissions (including those directly or indirectly related to RA, registered from the Hospital data base and selected by two rheumatologists from the research team) also had an influence on deaths as expected (3, 31). Regarding high disease activity, several publications have shown the impact on mortality (3, 5, 13, 26, 28, 30-32). We adjusted by the disease activity over time, as the average DAS-28 in each period. Consequently, this variable might have been reflected in our results as tendency to mortality but not as an independent factor.

Concerning other risk factors, possible associations between mortality and glucocorticoids, (as time-varying yes/no parameter), has been analysed by Mikuls *et al*. (5) and Jacobsson *et al*. (14). More recently, Listing *et al*. showed significant association between mortality and dose-related glucocorticoids (13). Our analyses have taken into account this variable, but it was dropped from the final model. This variable was defined in different ways in both studies; while Listing used it as the treatment with glucocorticoids during the last 12 months of each period, our study defined it as the average dose in the first three months of each period, explaining variations in the results.

Finally we also included other non-modifiable predictors of mortality, observing similar results to those previously published. Regarding demographic variables, older age at inclusion was also associated in our cohort with higher mortality rate, however being married was not included in the model (26-29, 32). In relation to other clinical related variables, presence of RF was also associated with mortality in the multivariate model, as in most previously published studies (3, 26, 29, 32-34).

Regarding our study limitations, we have to take into account the retrospective nature of the study. This, associated with the fact that data was recorded during routine consultations, that it is an environment with heavy workload, makes easier the possibility of incomplete and not recoverable information. This was the case of marital status, comorbilities and smoking habit with more than 40% of missing data. Thus, we did not include marital status in the final model. Regarding comorbilities and smoking habit, we tried to minimise this fact including the hospital admissions during the follow-up instead. For HAQ or DAS 28, such information was collected periodically during patient's appointments in our clinic, with trained nurses in specific consultations, every 6 months or every year. This fact translates, that some times the DAS28 was not available at any change of therapy in our patients. Consequently, to minimise missing values, we had to perform an averaged measure of these variables for the first year at different cut-off points of follow-up.

Unfortunately, our study did not include the causes of death; as such information was not recorded in the INDEF.

Another limitation of the study was the sample size, which has restricted the power to study potential differences between either different biological agents or different classical DMARDs, but we have been able to show the effects for the group of no therapy, BAs, other DMARDs and specifically MTX.

It is important to point out that this study was performed in clinical practice, and we have included a wide spectrum of RA patients with all possibilities of management, therefore our results are more likely to be generalised to other populations. Another strength of our study is that we have included changes in patient clinical and functional characteristics and treatment details at different time points during long-term follow-up, in order to achieve valid estimates of the risk of mortality. This approach is more robust than adjusting only for patient's baseline characteristics.

In conclusion, this study describes the mortality rate by therapy used in real-life conditions in an inception cohort of non-selected RA patients. After controlling for factors that influence mortality, we fail to show that survival in patients exposed to BA differ from those exposed only to other classic DMARDs, except for MTX that independently reduced the risk of death. Nevertheless, we have also seen that classical DMARDs and BA in general seem to be superior in reducing mortality than receiving no specific RA treatment, regardless of other factors. Perhaps this benefit can be more the result of early diagnosis and the introduction of effective and appropriate treatment strategies such as intensive (treat-to-target) management, full dose of disease DMARDs alone or in combination, and the emergence of BAs, all together, than a single component. Further studies should be necessary to discriminate by type of BA and DMARDs other than MTX on the survival of RA patients.

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