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Timing and impact of decisions to adjust disease-modifying antirheumatic drug therapy for rheumatoid arthritis patients with active disease

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Abstract

Objective—Guidelines recommend that rheumatoid arthritis (RA) patients with moderate to high disease activity (MHDAS) adjust disease-modifying antirheumatic drug (DMARD) therapy at least every 3 months until reaching low disease activity or remission (LDAS). We examined how quickly RA patients with MHDAS adjust DMARD therapy in clinical practice, and whether those who adjust DMARDs within 90 days in response to MHDAS reach LDAS sooner.

Methods—We identified RA patients with MHDAS in the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry, and conducted a competing risks regression on time to DMARD therapy adjustment and a Cox regression on time to LDAS.

Results—We identified 538 eligible subjects with 943.5 patient-years of follow-up. Sixty percent of patients with persistent MHDAS adjusted DMARDs within 90 days. Among all subjects, median times to DMARD adjustment and LDAS were 154 [IQR: 1–706] and 301 [140–706] days, respectively. Being elderly (subdistribution hazard ratio (SHR)=0.61, p=0.02), lower baseline

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disease activity (SHR=0.72, $p<0.01$), longer duration of RA (SHR=0.98, $p<0.01$), and biologic use (SHR=0.71, $p<0.01$) were significantly associated with longer times to therapy adjustment. African-American race (HR=0.63, $p=0.01$), higher baseline disease activity (HR=0.75, $p<0.01$), and not adjusting DMARD therapy within 90 days (HR=0.76, $p=0.01$) were associated with longer times to LDAS.

Conclusion—Adjusting DMARDs within 90 days was associated with shorter times to LDAS, but many patients with persistent MHDAS waited more than 90 days to adjust DMARDs. Interventions are needed to address the timeliness of DMARD adjustments for RA patients with MHDAS.

Key terms

rheumatoid arthritis; disease-modifying antirheumatic drug; treatment decisions; survival analysis

Introduction

Evidence-based guidelines recommend treating rheumatoid arthritis (RA) to the target of low disease activity or remission (LDAS) with disease-modifying antirheumatic drugs (DMARDs) (1–5). For patients with moderate to high disease activity (MHDAS), treat-to-target (T2T) guidelines recommend adjusting DMARD therapy at least every 3 months until LDAS is achieved (5). Clinical trials have shown that employing a T2T strategy leads to lower disease activity and reduction of progressive joint damage, compared to routine care (6). Furthermore, studies have demonstrated that improvements in these disease-specific outcomes are associated with reduced pain and improved physical function, health-related quality of life, and work productivity (6–8), suggesting that minimizing the amount of time RA patients spend with MHDAS is beneficial. Even brief periods of MHDAS (< 3 months) are associated with progression of joint damage and worsened short-term and long-term pain and functional deterioration (9–11). It is important to address delays in therapy adjustment for RA patients with MHDAS, which may increase the negative impact of the disease on current and future symptoms and quality of life.

Previous studies evaluating implementation of the T2T approach in trials and in clinical practice have reported the prevalence of therapy adjustment in response to MHDAS, but not the timing (12–17). Observational studies in the US have reported rates of therapy adjustment for patients with MHDAS ranging from 43–85% (14–15). The variation in these studies' results may originate from differences in the time frame used to evaluate the occurrence of therapy adjustment. Because the studies did not report times to DMARD adjustment, the percentage of therapy adjustments occurring within 3 months of the patient developing MHDAS is not known. To our knowledge, no other studies have examined how long it takes for RA patients with MHDAS to receive DMARD therapy adjustment, or the impact of timely DMARD adjustment on times to LDAS.

Our study assessed adherence to T2T in a clinical setting where predefined treatment protocols are not employed. Our main research questions were: 1) do RA patients with MHDAS receive DMARD adjustments in a timely manner, and 2) does timely DMARD adjustment reduce time spent with MHDAS? To examine these questions, we conducted

survival analyses of times to therapy adjustment and LDAS for RA patients using data from an observational registry.

Patients and Methods

Data source

The study used data for years 2010–2013 of the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry. RACER followed over 1000 RA patients seen at 4 University of Pittsburgh Medical Center (UPMC) rheumatology clinics from 2010–2016 (representing about 28% of all RA patients in the UPMC health system). Data on subjects' disease activity status, RA-related medications, and patient-reported outcomes (pain, functioning, and health-related quality of life) were collected at every clinic visit. The median [IQR] time between visits among RACER subjects was 3.5 [2.3–5.8] months. A list of current and new RA-related medications and dosages was verified by study coordinators at every visit in consultation with the patient, the electronic medical record, and the physician. Medications documented include biologic and nonbiologic DMARDs as well as corticosteroids. The RACER study was approved by the University of Pittsburgh Institutional Review Board, and subjects gave informed consent to participate in the registry.

Study Population

We selected patients with MHDAS according to the Disease Activity Score 28-joint with C-reactive protein (DAS28-CRP >3.2) (18) and medication data available at a baseline visit, and at least 1 subsequent visit with DAS28-CRP and medication data available.

Dependent variables

There were two dependent variables of interest: time to DMARD adjustment in response to MHDAS, and time to LDAS (DAS28-CRP ≥ 3.2), measured in days from the date of the baseline visit. DMARD adjustment was defined as adding, switching, or increasing the dose of DMARD medications (not including corticosteroids).

Independent variables

In all regression analyses, we controlled for factors that could impact the disease trajectory and treatment choice. Covariates included indicators for demographic characteristics (male gender and African-American race). African-American race was included because in previous analyses we found a negative association with decisions to adjust DMARDs in response to MHDAS. Constantinescu et al. (19) have also shown that African-American race is associated with increased perceptions of medication risk and lower perceptions of medication benefit in RA patients. We also included an indicator for elderly age (age ≥ 75) and a comorbidities covariate (Deyo-Charlson) because patients with elderly age and multiple comorbidities may have more restricted RA treatment options due to contraindications. The Deyo-Charlson index was included in regression analyses as a numerical variable (20, 21). Missing Deyo-Charlson index was imputed by carrying forward the most recent Deyo-Charlson value where possible. We included baseline RA disease severity (DAS28-CRP) and baseline RA disease duration (years), because patients with

higher disease severity and shorter disease duration may be treated more aggressively and adjust therapy sooner than patients with lower disease severity and longer disease duration. Patients with increased baseline disease severity and duration may also take longer to reach LDAS. We included baseline Short Form 12 mental and physical component summary scores (SF12-MCS and SF12-PCS), which document patient-reported mental and physical quality of life. The SF12-MCS and SF12-PCS may capture aspects of disease severity not reflected in the DAS28-CRP, which may affect decisions to adjust therapy and time to LDAS. We also included baseline use of a biologic DMARD, because in our previous analyses biologic use was associated with lower likelihood of DMARD adjustment in response to MHDAS.

The analysis of time to LDAS also included an indicator for adjusting DMARDs within 90 days in response to MHDAS (equal to 1 if therapy was adjusted in 90 days or less prior to reaching LDAS, 0 otherwise). We used a 90 day threshold to operationalize the recommendation that DMARDs should be adjusted at least every 3 months until the patient reaches LDAS (5). This allowed us to investigate whether timely therapy adjustment helps patients to reach LDAS sooner, controlling for other covariates.

Statistical Analyses

We performed descriptive analyses of the baseline characteristics of subjects included in regression analyses: age, gender, race, number of comorbidities, duration of RA, mental and physical quality of life (SF12-MCS and PCS), Multidimensional Health Assessment Questionnaire (MDHAQ) physical functioning component scores, and use of medications (biologics, corticosteroids, and nonbiologic DMARDs). We also described the percent of patients with their first follow-up visit within 90 days, distribution of time to DMARD adjustment and time to LDAS, percentage of patients who adjusted DMARDs within 90 days in response to MHDAS, and types of DMARD adjustments made.

We conducted survival analyses on time to DMARD therapy adjustment and time to LDAS for RACER subjects with MHDAS. First, competing risks regression using Fine and Gray's proportional subdistribution hazards model (22) was used to assess the impact of covariates on time to DMARD adjustment in response to MHDAS. The competing risks approach is appropriate because subjects are at risk for experiencing a secondary competing event (reaching LDAS) which changes their probability of experiencing the main event of interest (adjusting DMARDs in response to MHDAS) (23). A Cox regression approach, where the competing event is treated as a censored observation, can lead to biased estimates of covariate effects when the main and competing events are not independent (24). Fine and Gray's competing risks regression models the influence of covariates on the subdistribution hazards function, or the instantaneous rate of the event of interest among those who have not experienced the main event by time t (including those who experienced a competing event before time t). The regression model estimates subdistribution hazard ratios (SHR), which are interpreted as the ratio of the subdistribution hazard rates associated with two different levels of a covariate. A SHR greater than 1 indicates that the event of interest occurs at a faster rate for higher levels of the covariate, and that all else being equal, a subject with a higher level of the covariate would experience the event sooner. We defined DMARD

adjustment in response to MHDAS as the main event of interest and reaching LDAS before therapy adjustment as a competing event. Follow-up began when the subject was first known to have MHDAS (DAS28-CRP>3.2) and ended with one of three outcomes: 1) DMARD therapy adjustment before reaching LDAS (DAS28-CRP ≤ 3.2), 2) reaching LDAS before adjusting DMARD therapy, or 3) loss to follow-up (due to no further clinic visits observed, death, or withdrawal from the registry).

Second, a Cox proportional hazards regression was used to assess the impact of covariates on time to LDAS. Cox regression models the influence of covariates on the hazard function, or the instantaneous rate of the event of interest among those who have survived until time t . The Cox regression estimates hazard ratios (HR), which have an interpretation similar to that of the SHR described above. Here, the event of interest was reaching LDAS. Follow-up began when the subject was first known to have MHDAS and ended when 1) the subject reached LDAS, or 2) when the subject was lost to follow-up (due to no further clinic visits observed, death, or withdrawal from the registry).

For all regression analyses, we included subjects adjusting therapy at the baseline visit by resetting their survival time to 1 day.

Sensitivity analyses were conducted to examine how including corticosteroid adjustments in the analysis would affect the results. Use of corticosteroids for the treatment of RA varies among different communities of rheumatologists around the world; while in the US corticosteroids are not generally considered a long-term treatment solution, in other practice communities corticosteroids may be used with DMARDs to control RA disease activity.

Results

Out of 1041 RACER registry participants, 558 met eligibility criteria, representing a total of 943.5 patient-years of observation. The average follow-up time for each subject was 617 days. The clinic visit dates for these subjects spanned between February 2010 and November 2013. Tables 1 and S1 (Supplementary materials) show baseline characteristics and Deyo-Charlson scores of subjects.

The regression analyses included 543 subjects with complete data on covariates. A flowchart (Figure 1) illustrates inclusion/exclusion of subjects for the regression analyses.

The status of the 558 subjects (MHDAS, DMARD adjustment in response to MHDAS, or LDAS) was plotted over time in Figure 2, while a survival plot of time to LDAS is shown in Figure 3. By the end of follow-up for the 558 subjects, 60.8% of subjects (n=339) adjusted DMARDs in response to MHDAS, 31.7% of subjects (n=177) reached LDAS before adjusting DMARDs, and 7.5% (n=42) remained with MHDAS. Among the 42 subjects lost to follow-up before adjusting DMARDs in response to MHDAS or reaching LDAS, 40 did not have further follow-up visits documented, 1 died (after 158 days of follow-up), and 1 withdrew from the registry (after 364 days of follow-up). The median time [IQR] that subjects awaited DMARD adjustment (n=558, 339 events) was 154 days [1–706]. The median time to LDAS (n=558, 398 events) was 301 days [140–706].

For 44.8% of subjects, the first follow-up visit occurred within 90 days of the baseline visit. Table S2 (Supplementary materials) shows the distribution of time spent awaiting DMARD adjustment. Among all 558 subjects with MHDAS, 56.7% waited more than 90 days to adjust DMARD therapy. Among 403 subjects with persistent MHDAS (i.e. the patient does not reach LDAS before therapy adjustment), 40% waited more than 90 days to adjust DMARD therapy.

Among all DMARD adjustments documented (Supplementary materials, Table S3), initiating new DMARDs (66%) was more common than increasing the dose of existing DMARDs (34%). Initiating new DMARDs was more common among DMARD adjustments taking place within 90 days of the baseline visit (71%) than among adjustments taking place more than 90 days later (51%), while the reverse trend was seen for dose increases.

The results of regression analyses (n=543) are shown in Table 2. For the competing risks regression, the following covariates were significantly associated with longer times to DMARD adjustment in response to MHDAS, taking into account the competing risk of reaching LDAS before DMARDs were adjusted (subdistribution hazard ratio (SHR), p-value): being elderly (SHR=0.61, p=0.02), having lower disease activity at baseline (SHR=0.72, p<0.01), having a longer baseline RA disease duration (SHR=0.98, p<0.01), and use of a biologic DMARD at baseline (SHR=0.71, p<0.01). Sex, African-American race, number of comorbidities, and SF12-MCS and SF12-PCS at baseline were not significantly associated with time to DMARD adjustment in response to MHDAS. The estimated cumulative incidence function of DMARD adjustment in response to MHDAS is shown in Figure 4.

For the Cox regression of time to LDAS, the following covariates were significantly associated with longer times to LDAS (hazard ratio (HR), p-value): being African-American (HR=0.63, p=0.01), having higher disease activity at baseline (HR=0.75, p<0.01), and not adjusting therapy within 90 days (HR=0.76, p=0.01). In addition, higher baseline SF12-MCS (HR=1.01, p=0.03) and higher baseline SF12-PCS (HR=1.01, p=0.02) were significantly associated with shorter times to LDAS. Elderly age, sex, number of comorbidities, disease duration at baseline, and use of biologic at baseline were not significantly associated with time to LDAS.

Sensitivity analyses

Even when corticosteroid adjustments were included in the analyses, regression results remained robust (see Supplementary materials, Table S4). For the competing risks analysis of time to DMARD adjustment, including corticosteroid adjustments increased the number of events from 339 to 381, but did not change results for any covariates except for elderly age, which was no longer significantly associated with longer times to DMARD adjustment in response to MHDAS.

Inclusion of corticosteroid adjustments slightly increased the proportion of subjects that adjusted therapy within 90 days from 43% (n=242) to 48% (n=267), and the Cox regression results for the analysis of time to LDAS were robust to this change.

Discussion

While the majority of subjects with persistent MHDAS received DMARD adjustment within 90 days, 40% waited more than 90 days for DMARD adjustment, and 32.3% waited more than 180 days to adjust DMARDs. Furthermore, we found that adjusting DMARDs in response to MHDAS within 90 days was associated with shorter times to LDAS. Our results suggest that timely DMARD adjustment reduces the time patients spend with MHDAS, and that delays in DMARD adjustment are an important issue in care for RA patients which needs to be addressed.

While 44.8% of subjects had their first follow-up visit within 90 days, it is possible that difficulty in scheduling follow-up visits contributed to delayed DMARD adjustment for some subjects. Follow-up visits were scheduled at the discretion of physicians and patients; patients were also able to request earlier follow-up visits if needed. In theory, it was possible for all patients with MHDAS to have a follow-up visit within three months (indeed, some patients even returned within one month). Among all RACER patients, the median [IQR] time between visits was 3.5 [2.3–5.8] months; 38% of patients were followed-up within three months. Patients with MHDAS had shorter follow-up times (3.0 [2.0–4.6] months) and higher rates of follow-up within three months (51%) compared to patients with LDAS (4.1 [3.0–6.2] months; 26% followed-up within three months). Nevertheless, capacity to schedule follow-up visits may be an important contributor to delayed DMARD adjustments and should be assessed in future studies.

We found that having lower disease activity at baseline, use of biologics, having longer disease duration, and being elderly were associated with longer times to DMARD adjustment in response to MHDAS (however, elderly age was no longer associated when corticosteroid adjustments were included in the analysis). These results illuminate four factors potentially contributing to delayed DMARD adjustment among patients with MHDAS:

1. On average, DMARDs were adjusted less aggressively for patients with less severe disease activity.
2. Those taking biologics did not adjust therapy as quickly, perhaps due to the difficulty of obtaining payer approval for a new biologic, or more time needed to assess therapeutic effect. The latter mechanism is supported by Tymms et al. (25), where rheumatologists reported not escalating DMARD therapy for patients with active disease due to “insufficient time to assess response to recently initiated DMARDs” in 9.2 % of cases.
3. MHDAS in elderly patients was often addressed with adjustment of corticosteroids rather than DMARDs.
4. DMARDs were adjusted less aggressively for patients with longer disease duration. Such patients may have fewer therapeutic options available. In addition, the attribution of symptoms to irreversible joint damage may discourage DMARD adjustment, since DMARDs can only address symptoms due to inflammation, not irreversible joint damage. Counter to our findings, Kievit et al.

(26) found that disease duration was one of the least influential factors in rheumatologists' decisions about escalating therapy, when presented with a hypothetical treatment scenario. However, Tymms et al. (25) found that in 19.7% of cases where DMARD therapy was not adjusted in spite of the patient having MHDAS, rheumatologists indicated "irreversible joint damage" as a barrier to optimal disease control.

Studies of adherence to a T2T strategy (12–13, 17) and surveys of rheumatologists (25–26) have identified barriers to DMARD adjustment for patients with MHDAS consistent with our findings, such as physician disagreement with the disease activity index, irreversible joint damage, non-inflammatory musculoskeletal pain, older patient age, and insufficient time to assess recently initiated DMARD. Additional barriers to DMARD adjustment are medication nonadherence and patient preference not to escalate therapy. RA patients often have concerns about the risks of medications (27–29) and prefer not to treat their disease aggressively (27–30).

Our study identified two new barriers to DMARD adjustment: use of biologics and lesser disease severity. Kievit et al.'s (26) survey of rheumatologists using hypothetical treatment scenarios indicated that rheumatologists may be less willing to adjust biologics for patients with lower disease activity measures—this suggests that further research is needed to explore how different barriers to DMARD adjustment are interrelated. It would also be useful to determine the relative importance of physician- and patient- related factors in decisions not to adjust DMARDs when the patient has MHDAS, and how this varies with disease severity.

We found that African-American race, higher baseline disease activity, lower SF12-MCS and SF12-PCS, and not adjusting DMARDs within 90 days were significantly associated with longer times to LDAS. African-American race may be associated with greater delays in reaching LDAS due to poorer access to health care providers and treatments, or possibly poorer medication adherence. Constantinescu et al.'s study (19) of the relationship between race and treatment preferences in RA patients found that African-Americans were more likely than whites to be risk averse and assigned greater importance to the risks of medications, while whites focused more on the benefits of medications. Suarez-Almazor et al. (31) also found that newly diagnosed non-white RA patients took longer than white RA patients to initiate DMARDs after onset of symptoms. This suggests that race may have complex effects on treatment decision-making and subsequent outcomes for RA patients. Patients with greater disease activity and lower SF12-MCS and SF12-PCS at baseline may take longer to attain LDAS because their RA is more resistant to treatment. Self-reported mental and physical functioning on the SF12 may capture additional aspects of disease severity not accounted for by the DAS28-CRP. Controlling for other covariates, adjusting DMARDs within 90 days in response to MHDAS was associated with a higher likelihood of reaching LDAS during follow-up. This provides further evidence from clinical practice that timing of DMARD adjustments affects how soon RA patients achieve LDAS, and indicates that attention to timing is important in implementing treat-to-target guidelines in RA.

Promoting T2T in clinical practice requires coordinated change at the system, rheumatology practice, and individual levels. This was demonstrated in two recent trials testing multilevel interventions to implement T2T in RA at US rheumatology practices (32, 33). Researchers engaged participating rheumatology practices and physicians to implement the following conditions:

1. Setting and maintaining documentation of a treatment target
2. Assessment and documentation of disease activity at all visits
3. Documented engagement of patients in shared decisions about targets and treatments
4. Mandated DMARD adjustment if the patient has active disease/has not reached the treatment target, *or* documenting reason if treatment is not adjusted
5. Mandated minimum visit frequency (depending on whether the patient has active disease)

In the RACER registry, only the second condition, routine assessment and documentation of disease activity, was met. Our findings suggest that condition 5 may be especially important for improving timely DMARD adjustment for patients with MHDAS. Fifty-five percent of patients in our study did not have a follow-up visit within three months. Condition 3, engaging patients in shared decisions about targets and treatments, may also be critical for reducing delays to recommended DMARD adjustments. The results of the Corrona T2T trial (33) and previous studies (12, 17, 25) indicated that patient reluctance is a common barrier to DMARD adjustment. Finally, as our study found that biologic use was associated with delayed DMARD adjustment, streamlining the process for obtaining access to biologic treatments at the payer and practice level may also help ensure that patients receive the most effective treatment as quickly as possible.

Our analysis has some limitations worth noting. The study cohort was drawn from a registry based at a single metropolitan center in the US. Access to care (medications and rheumatology appointments) and prescribing practices may be different in other settings, limiting the generalizability of our study findings. We lacked data to assess the impact of patient and physician preferences on the timing of treatment decisions. The Deyo-Charlson index may not fully capture cases where DMARD escalation is contraindicated. Future studies should account for medical circumstances that might impede DMARD adjustment, such as comorbid conditions, medical procedures, or contraindications with other non-RA medications. Finally, for 63% of the eligible subjects, follow-up began at the first RACER visit; thus, it is not known whether they had MHDAS at previous visits as well. If some subjects had persistent MHDAS prior to enrollment in RACER, their times to therapy adjustment and LDAS would be understated, possibly biasing our regression results. However, we did not expect systematic differences between subjects with MHDAS first documented at their first RACER visit or at later visits, since recruitment for RACER was not based on any clinical characteristics other than having a diagnosis of RA. Our study's estimate of the median time to therapy adjustment and time to LDAS should be considered conservative.

The results of our survival analyses suggest that delays in DMARD adjustment of more than 3 months are common among RA patients with MHDAS, highlighting an important potential gap in quality of care for these patients. Delays in therapy adjustment were associated with elderly age, less severe disease, longer duration of RA, and biologic use. Our results also suggest that among patients with MHDAS, those who adjust DMARDs within 3 months achieve LDAS sooner, while African-American patients may experience delays in achieving LDAS. Further investigation is needed to understand how and why biologic use is associated with delayed DMARD adjustment, as well as how race affects disease outcomes for RA patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and Innovations

- This is the first study to examine time to DMARD therapy adjustment and time to low disease activity (LDAS) for RA patients with moderate/high disease activity (MHDAS), as well as the factors associated with delayed therapy adjustment and low disease activity.
- Forty percent of subjects with persistent MHDAS waited more than 90 days for DMARD therapy adjustment, suggesting that many RA patients may not be receiving timely therapy adjustment in clinical practice.
- Adjusting DMARDs within 90 days in response to MHDAS was associated with a higher likelihood of reaching LDAS during follow-up. This indicates that attention to timing is important in implementing treat-to-target guidelines in RA.

Figure 1.
Inclusion/exclusion for regression analyses

Figure 2.
Status plot of subjects over time

Figure 3.
 Survival plot of time to low disease activity/remission (n=558)*
 *Hash marks indicate censored subjects.
 MHDAS = moderate/high disease activity.

Figure 4. Competing-risks regression: estimated cumulative incidence of DMARD adjustment in response to moderate/high disease activity

Table 1

Baseline characteristics of subjects

Characteristic	Mean (SD) or %	n
Age in years	59.8 (12.9)	558
Age ≥ 75	11.1%	558
Female sex	79.4%	558
African-American	11.5%	558
Deyo-Charlson index	1.9 (1.4)	557
DAS28-CRP	4.3 (1.0)	558
Duration of RA	14.7 years (13.2)	558
SF12 mental component score ⁺	46.8 (11.5)	544
SF12 physical component score ⁺	35.0 (10.0)	544
MDHAQ physical functioning component score [#]	2.7 (1.8)	544
On biologic	38.9%	558
On corticosteroids	60.4%	558
On nonbiologic DMARDs	80.5%	558
On biologic monotherapy	12.7%	558
On any DMARD (biologic or non-biologic)	93.2%	558
On combination therapy (biologic and non-biologic DMARD therapy)	26.2%	558

⁺ Reported on a scale of 0–100.

[#] Reported on a scale of 0–10.

Table 2

Rheumatoid arthritis patient characteristics associated with time to DMARD adjustment in response to moderate/high disease activity (MHDAS) and time to low disease activity/remission

Parameter	Competing risks regression: Time to DMARD adjustment ⁺		Cox regression: Time to LDAS	
	n=543 331 main events 172 competing events 7.4% censored [#]		n=543 387 events 28.7% censored [#]	
	Subdistribution hazard ratio	P-value	Hazard ratio	P-value
Age at baseline 75	0.61	0.02	1.05	0.77
Male	0.90	0.37	1.08	0.56
African-American	0.85	0.30	0.63	0.01
Deyo-Charlson	0.99	0.77	1.00	0.96
DAS28-CRP at baseline	1.40	<0.01	0.75	<0.01
Disease duration at baseline	0.98	<0.01	0.99	0.18
SF12-MCS at baseline	1.00	0.30	1.01	0.03
SF12-PCS at baseline	1.00	0.50	1.01	0.02
Using biologic at baseline	0.71	<0.01	1.07	0.56
Adjusted therapy in 90 days -	-	-	1.32	0.01

⁺The main event of interest was DMARD adjustment in response to active disease, while the competing event was reaching LDAS before adjusting DMARDs. DMARD therapy adjustment was defined as adding, switching or increasing dose of biologic or nonbiologic DMARD therapies.

[#]Subjects who had not achieved the outcome (adjusted DMARD therapy or exited active disease) by the end of followup were marked as censored.