The 20 year outcome and association between early treatment and mortality and disability in an inception cohort of patients with rheumatoid arthritis: results from the Norfolk Arthritis Register

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Abstract

Objective – To describe the outcome of patients with rheumatoid arthritis (RA) over 20 years from symptom onset; to assess the association between early treatment (DMARDs/steroids) and mortality and disability over follow-up.

Methods – Patients from the Norfolk Arthritis Register recruited from 1990-94 who met the 2010 ACR/EULAR RA criteria at baseline were included in this analysis. Demographic/clinical variables were collected at baseline and years 1-3, 5, 7, 10, 15 and 20. Disease activity (swollen/tender joint counts (SJC/TJC)), disability (HAQ) and mortality over 20 years are described. Association between treatment group (early treatment (ET) = treatment ≤6 months after symptom onset; late treatment (LT) = treatment >6 months; never treatment (NT) = no treatment) and mortality and disability were assessed using weighted pooled logistic regression and weighted multilevel mixed-effects linear regression respectively. Inverse weights were used to account for indication/censoring confounding.

Results – This study included 602 patients with RA (median (IQR) age = 56 (44, 68) years; 65.9% women). Median disease activity was low over follow-up (SJC 1-3, TJC 3-6). Median HAQ rose after year 1 but remained at low/moderate levels (median 1.25 after year 10). There was reduced mortality risk in the ET and LT compared to NT group. ET group had comparable HAQ to NT group over follow-up (β 0.03, 95% CI -0.06, 0.12); LT group had increased disability (LT vs NT β 0.10, 95% CI 0.02, 0.17).

Conclusion – This study indicates the importance of early treatment regarding long-term outcomes of patients with RA.

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Early rheumatoid arthritis (RA), a subset of inflammatory polyarthritis (IP), is a chronic disease primarily characterised by synovial joint inflammation (1). Both conditions may lead to progressive joint destruction and premature mortality (2-5). However, with appropriate therapy outcome can potentially be ameliorated (6-8), although there are relatively few studies investigating the long-term outcome of patients with RA (9-16). One UK study recruited 112 patients with prevalent RA between 1964-6 (mean age at symptom onset 45 years). Twenty years later, 35% of these patients had died and a further 43% were in moderate / high functional disability classes (17). The patients in this cohort were predominantly treated with steroids, gold and chloroquine; standard treatments at that time.

Gathering new data on outcomes in the modern era is important because, over the last two decades, there have been significant advances in available treatments and strategies for the management of RA (18,19). Methotrexate (MTX) has become the first choice synthetic disease modifying anti-rheumatic drug (sDMARD) (18), and a number of biologic DMARDS (bDMARDs) have been introduced since 2000 (20). Previous research in patients with RA has demonstrated an association between reduced mortality risk and ever exposure to MTX treatment over a mean of six years (6), reduced mortality risk and exposure to tumour necrosis factor inhibitor (TNFi) treatment over a mean of 4.9 years (21), as well as improved functional disability with MTX and TNFi therapy (22-25).

The aforementioned advances in treatment strategy included a shift towards initiating sDMARD therapy early in the disease course, aiming to treat patients within a "window of opportunity" in order to achieve maximal beneficial outcome (26,27). We have previously shown that patients with early inflammatory arthritis who received early sDMARD or steroid

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treatment (initiation <6 months after symptom onset) had comparable odds of having high HAQ scores (≥1) at five years to patients who never required treatment, after adjusting for differences in disease severity between the treatment groups. Those who initiated therapy later (≥6 months after symptom onset) had two-fold increased odds of having high HAQ compared to those who were never treated (28). Furthermore those treated early showed a reduction in HAQ scores from baseline to year 10, which approached significance, whilst those treated later had increased HAQ scores at year 10 compared to baseline, again after adjusting for differences in disease severity between groups (29). Other groups have also shown the negative consequences of delayed assessment in terms of remission rates and joint destruction (30). However the benefits of early treatment have yet to be demonstrated to extend past 10 years. It is also possible that the underlying natural history of RA may have changed over time (31).

This study describes the outcome of patients with early RA over the course of 20 years; including mortality, disease activity and physical function. This study also examined the relationship between early sDMARD or steroid therapy and mortality risk and physical function over 20 years.

PATIENTS AND METHODS

In total, 1098 patients with IP were recruited to the Norfolk Arthritis Register (NOAR) between 1990 and 1994. Detailed information on NOAR can be found elsewhere (32). In brief, NOAR aimed to recruit and follow prospectively all incident cases of patients presenting with IP in the former Norwich Health Authority region, Norfolk, UK. Patients were referred by primary care physicians (a large majority of UK patients are registered with a primary care practice (~99%)) or consultant rheumatologists. Inclusion criteria were: ≥16

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years old, and ≥2 swollen joints lasting ≥4 weeks. Patients were excluded from this analysis if they were recruited more than two years following symptom onset (patients excluded = 76). For this analysis, only patients who met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA were included (33). The criteria were applied retrospectively to the baseline characteristics of the patients (patents with RA included = 614). Patients gave written consent and the study was approved by the Norfolk and Norwich University Hospital Local Research Ethics Committee.

Assessments*:* Patients were assessed at baseline and at 1, 2, 3, 5, 7, 10, 15 and 20 years after registration. Patients were only assessed beyond year five if they had documented swollen joints on two or more occasions or had received DMARDs or oral corticosteroids by the fifth year assessment (N excluded = 8). Date of birth and gender were recorded at baseline. At each assessment research nurses administered a standardised questionnaire (including smoking status (current / ex / never)). Start and stop dates of all DMARDs and steroids were collected from patients at each follow-up. Patients who were taking sDMARDs or steroids before symptom onset were excluded from the analysis (N = 12). Patients were classified into one of three treatment groups, with treatment being sDMARDs and steroids: received treatment ≤6 months after symptom onset = early treatment (ET), received treatment >6 months after onset = late treatment (LT), never received treatment = never treatment (NT). Comorbidities were self-reported at and after baseline and were coded based on the relevant chapters of ICD9/ICD10 (supplementary file 1). Once a patient reported a comorbidity they were coded as having that comorbidity throughout the rest of their follow-up. Research nurses performed 51 swollen and tender joint counts (SJC / TJC), from which 28 joint counts were derived, apart from follow-ups five and seven. Blood

samples were taken at baseline. Serum was stored, frozen, for determination of C-reactive protein (CRP; mg/l), rheumatoid factor (RF; latex test, positive cut-off 40 units/ml) and anti-cyclic citrullinated peptide antibodies (Anti-CCP2; tested using the Axis-Shield, Dundee, UK Diastat Anti-CCP kit, cut off 5 units/ml). Blood samples were then taken every five years, from which only CRP was determined. The three component (28 SJC/ 28 TJC/ CRP) Disease Activity Score (DAS28) was calculated (34) for assessment where a CRP result was available.

Outcomes: Disease activity was analysed based on 51 SJC and 51 TJC as described above. All patients were flagged with the Office for National Statistics (ONS), the holders of the UK death register, who provided copies of death certificates including date of death and underlying cause of death. The ONS also provided age and sex specific mortality rates by calendar year for the Norfolk population (1990-2013). Patients were censored at their 20th anniversary assessment or 20 years after symptom onset if they did not attend the 20th assessment, other than patients who left the country who were censored at their departure date (N = 7 patients with RA). At each assessment patients completed the British version of the Health Assessment Questionnaire – Disability Index (HAQ) (35), a validated self-report measure of functional disability which yields a score from 0 (no disability) to 3 (maximum disability).

Statistical analysis: Descriptive statistics were used to describe baseline demographic and clinical variables. Baseline scores were compared between treatment groups using Kruskal-Wallis or Chi squared tests, depending on the type and distribution of data.

The standardized mortality ratio (SMR) was calculated for the cohort by comparing observed numbers of deaths to expected number of deaths for the local population based on age and sex specific mortality rates. Patients were included in this analysis until death, 20

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years after symptom onset or the end of 2013, whichever came first. The association between baseline variables, including age, gender, SJC/TJC(51), HAQ, CRP, RF and anti-CCP2, and mortality was assessed using a multivariate Cox proportional hazards model. To assess the association between treatment group and mortality, initially a Cox proportional hazards model, adjusted for age and gender, was used and Kaplan-Meier survival curves were plotted. The SMR for each treatment group was also calculated. To account for confounding by indication a weighted multivariate pooled logistic regression model was used (36,37), which gives odds ratios that are equivalent to hazard ratios. Covariates included baseline measures (gender, smoking status, RF, anti-CCP, HAQ, SJC51, TJC51, CRP) and time-varying measures where collected (HAQ, SJC51, TJC51, CRP, comorbidities).

Median SJC51, TJC51 and HAQ scores and number and proportion of patients taking sDMARDs are reported for each time-point. The relationship between treatment group and disability over 20 years was assessed using a multilevel mixed-effects linear regression model, a longitudinal regression model which allows time-varying weights. Initially only age and gender were controlled for using an unweighted model. To account for confounding by indication and censoring, a weighted multivariate model was then used, with the same covariates as the pooled logistic regression described above (barring time-varying HAQ).

To control for confounding by indication and censoring, inverse probability weights, which account for cumulative treatment exposure as well as censoring were used to weight the covariates in the regression models (supplementary file 2), using methods adapted from Fewell et al (36). Multiple imputation, using iterative chained equations (five imputed datasets created) conditioned on baseline, lagged and current assessment variables, was used to account for missing data on assessments which patients attended. All regression

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analyses were also performed on the total IP population (N=1000). Analysis was performed using Stata 13.1 (Stata Corp, College Station, TX, USA).

RESULTS

A total of 602 patients with RA were recruited from 1990-1994 and met all inclusion / exclusion criteria (median symptom duration 5.4 months (inter quartile range (IQR) = 2.9, 9.9)). Median age at symptom onset was 56 years (IQR = 44, 68) and 397 (65.9%) patients were women. Baseline characteristics are shown in Table 1.

In total, 160 (26.6%) patients received treatment within 6 months of symptom onset. Of these, 94 (58.8%) were prescribed sulfasalazine (SSZ), 45 (28.1%) were prescribed steroids, 8 (5.0%) were prescribed MTX and 13 (8.1%) were prescribed other DMARDs. Of the remaining patients, 88 (19.9%) received their first treatment within 6-12 months, 77 (17.4%) 1-2 years and 84 (19.0%) ≥two years after symptom onset, leaving 193 (43.7%) patients who never received treatment whilst attending follow-up. Males were more likely to receive ET compared to LT (number (% of total group) male: ET = 75 (46.9%), LT = 49 (27.7%)) and patients who received ET had shorter disease duration at presentation than those who received LT (symptom duration at baseline (months): ET = 2.7, LT = 7.4). Patients who received ET had worse clinical characteristics on all baseline variables compared to LT and NT, other than tender joint counts and autoantibody status (see Table 1). Similar results were seen when including all IP patients (see supplementary file 3 for details).

20 years of follow-up: 207 patients (34.4%) were seen for a 20 year assessment. During the follow-up period 205 patients (34.1%) left the cohort due to death, 135 (22.4%) declined

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further follow-up visits, 8 (1.3%) became ineligible at year 5 and 47 (7.8%) were lost to follow-up (supplementary file 4 for further details).

As all patients were flagged with the ONS, mortality data were complete for the whole cohort up to 20th anniversary assessment (even if follow-up ceased), other than those who left the country. Over 9,774 person years of follow-up (mean = 14.8 years), 265 (44.0%) patients died. The age and sex standardised SMR for the cohort of patients with RA was elevated compared to the general population in the Norfolk area (SMR = 1.25, 95% CI 1.11, 1.42). In a multivariate Cox regression, older age at symptom onset (HR 1.10 per increased year of age at onset, 95% CI 1.08, 1.11) and male gender (HR 1.47, 95% CI 1.13, 1.92) were associated with increased risk of death during that time period. Being a current smoker at baseline was independently associated with an increased risk of death compared to never smokers (HR 1.65, 95% CI 1.17, 2.33) and ex-smokers (HR 1.82, 95% CI 1.34, 2.45).

In total, 88 (55.0%) of the patients who received ET died over the course of follow-up compared to 99 (39.8%) LT and 78 (40.4%) NT. The SMR was elevated in the ET (ET SMR: 1.28, 95% CI 1.03, 1.59) and the LT group (LT SMR: 1.23, 95% CI 1.01, 1.51) and there was a trend towards significance for the NT group (NT SMR: 1.25, 95% CI 0.99, 1.57) compared to the general population of Norfolk. Within the cohort, there was little difference in the risk of death between treatment groups, after adjusting for age and gender (ET vs NT HR 1.09, 95% CI 0.80, 1.11; LT vs NT HR 0.99, 95% CI 0.73, 1.33) (Figure 1). After weighting to account for confounding by indication the association between time to first treatment and mortality risk remained non-significant for the ET group, although there was a trend towards reduced risk of mortality (ET vs NT OR_{adj} 0.78, 95% CI 0.54, 1.11; LT vs NT OR_{adj} 0.66, 95% CI 0.47, 0.92).

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Including all patients with IP (N=1000) showed similar results (ET vs NT OR_{adj} 0.82, 95% CI 0.61, 1.11; LT vs NT OR_{adj} 0.78, 95% CI 0.59, 1.03).

Table 2 shows the median disease activity and functional disability over follow-up for the patients with RA, stratified by treatment group. All patients were included in the analysis up to the point of their last follow-up. Median SJC and TJC fell rapidly in the first year after baseline (baseline median SJC = 11, TJC = 14) and remained low throughout follow-up (median SJC ranged from 1-3, median TJC ranged 3-6). Median HAQ scores for the total cohort also fell initially, but then increased from the year two assessment onwards, culminating in a median score higher than baseline after year 7 (median (IQR) HAQ after year 10 = 1.25 (0.50, 2.00)) (Figure 2). The proportion of patients taking sDMARDs was higher in the ET group compared to the LT group up to assessment 2, after which the proportions were comparable (55-65%, see Table 2). Only a small proportion of patients took bDMARDs during the study (7.6%) and these patients were evenly spread between the ET and LT groups (ET = 19/160 (11.9%); LT = 27/249 (10.8%)). Similar trends were seen when including all patients with IP, although with lower median scores due to lower disease severity in this group (see supplementary file 3 for these results).

Swollen and tender joint counts were similar between treatment groups over follow-up, excluding baseline assessment. However functional disability was consistently higher in patients who received treatment compared to patients who did not (Table 2).

After controlling for age and gender, there was an association between being prescribed treatment and increased HAQ scores over follow-up (Table 3). When the model was fully adjusted and inverse probability weights were applied to account for confounding by indication, patients who received ET had similar disability over follow-up to NT patients (ET

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vs NT β 0.03, 95% CI -0.06, 0.12), whereas those who received LT had significantly higher disability over follow-up (LT vs NT β 0.10, 95% CI 0.02, 0.17). Similar results were seen when including all patients with IP in the analysis (see Table 3).

DISCUSSION

This paper has two important messages, firstly about the long-term outcome of patients with RA in the modern era treated according to best practice at the time of presentation; secondly about the benefit of early treatment which is still apparent into the second decade after symptom onset with respect to functional disability.

Median swollen and tender joint counts fell after baseline and remained low over follow-up. Median functional disability fell initially, but then rose over time to above baseline levels by year 7 and then continued to rise to year 20. Kapetanovic et al followed 183 Swedish patients with early RA for 20 years and showed a similar HAQ trajectory, with mean HAQ scores rising to above 1.0 at year 10 and beyond (13). This functional disability is higher than reported for healthy individuals of a similar age. In a random sample of the population from central Finland, mean HAQ scores for all age groups below 75 were <0.5 (38). Similar results were reported from a random sample of the older population (aged >65 years) of Augsburg and Aichach-Friedberg, Germany (only 22.5% of the cohort had a HAQ score ≥ 0.5) (39).

Despite this increase in median HAQ scores over 20 years, these results are encouraging. A score of 1.38 represents low to moderate disability (40). By contrast, a study which recruited 112 patients with RA in Droitwich, UK from 1964-1966 and followed them for a similar time period reported much higher levels of disability at 20 years (17). It thus appears that long-term disability in RA patients is now less severe. Furthermore, whilst a similar

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proportion of patients died in the Droitwich and NOAR studies, patients in the NOAR cohort had an older mean age at onset (56 vs 45 years).

The second finding from this paper relates to the benefits of early DMARD therapy. We have previously shown that treatment within the first six months following symptom onset is associated with benefits in physical function at five and ten years, after appropriate adjustment for differences in disease severity (28,29). In this analysis we found that, after adjusting for confounding by indication (i.e. adjusting for demographic and disease factors which may have influenced the decision to start DMARD or steroid treatment at baseline or subsequently), patients who were treated early had similar levels of disability over follow-up to those who did not receive treatment, whilst patients treated later had significantly higher levels of disability over 20 years. This supports the importance of the "window of opportunity" construct for treatment, showing that early treatment leads to improved outcomes even into the second decade following symptom onset. Increased functional disability over time could be due to worse joint damage (41,42), and it has been shown that those who receive later treatment have higher radiological scores at follow-up than those treated early (8,43,44).

The SMRs for the total population and for the two treatment groups were elevated. The SMR for those who were never treated was elevated to a similar extent, but failed to reach significance. There was a trend towards reduced mortality risk in the ET group and a significant reduction in mortality risk in the LT group compared to NT. Treatment with MTX has previously been shown to be associated with reduced risk of mortality in RA patients in the medium term (6), and we have shown previously that being in remission on at least one of three annual assessments after baseline was associated with reduced mortality risk in

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patients with IP compared to those who were not in remission at any of the three assessments over a median of 7.1 years (45). It is the nature of the SMR that it approaches 1.00 as follow-up increases as all patients will eventually die.

This analysis has a number of strengths. It is one of the largest inception cohorts of patients with RA and IP with a follow-up of 20 years. By retrospectively applying the 2010 RA criteria we have been able to study the subgroup of patients classified as having RA according to the latest criteria and compare their results with the whole NOAR cohort and with other published RA cohorts. The use of inverse probability weights to a longitudinal regression model allows us to control for confounding by indication over time. This is the current state-of-the art in terms of controlling for confounding by indication and differs from approaches taken in our previous work (28,29).

The attrition rates for this cohort are to be expected over 20 years of follow-up. The use of inverse probability of censoring weights minimises attrition bias. SJC and TJC were not measured at follow-ups five and seven, meaning that these time-points could not be included in the longitudinal analyses. However as we assessed a majority of these patients at assessments three and ten, patients' disability should be modelled sufficiently. A surprisingly high proportion of patients (32.1%) never received DMARDs or steroids. This reflects the fact that patients were recruited from primary and secondary care and followed regardless of disease severity. If the study had been entirely based on continuing follow-up in secondary care then patients with mild disease would have been discharged and contribute no follow-up information. Our study shows that patients who never received DMARD treatment did well and served as a useful comparison group for those who were treated either early or late. Lastly, these patients were recruited over 20 years ago, meaning

that the standard treatment at the time does not reflect best treatment practices today. Whilst this is a limitation of this project, treatment practices are constantly evolving. If we wish to understand the 20 year outcome of RA patients, the only way to do this is to study patients who were exposed to the treatment strategies of 20 years ago. Nevertheless, these results are still important as they show a clear improvement from patients studied in the 20 year period before this, and that early treatment with predominantly SSZ or steroids is associated with improved outcomes 20 years later. Thus, as MTX is considered a more effective treatment than SSZ, the benefits 20 years later of early treatment with MTX may be even greater.

In conclusion, this cohort of RA patients had relatively low levels of median disease activity from year one onwards. In contrast median disability rose to above baseline levels after 7 years. This disability is still moderate, thus on average patients experienced relatively good long-term outcomes, particularly compared to an earlier UK cohort recruited from 1964-66 and followed for 20 years. As might be expected ET was given to patients with more severe disease. After adjusting for this confounding by indication over time, functional disability was higher in the LT group compared to the NT group over the course of follow-up, whilst the ET group had similar levels of disability to the NT group indicating that the benefits of early treatment were sustained into the long-term.

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Contributors: Review of manuscript: JMG, DPMS, AJM, JRC, TM, ML, SMMV; study concept and design: JMG, DPMS, ML, SMMV; acquisition of data: JRC, TM; analysis and interpretation of the data: JMG, DPMS, ML, SMMV.

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TABLES

Table 1 – Baseline characteristics of the cohort of patients with RA

	Cohort (N=602) Median (IQR) [% complete data]	ET (N=160) § Median (IQR) [% complete data]	LT (N=249) § Median (IQR) [% complete data]	NT (N=193) § Median (IQR) [% complete data]	p*
Age at onset, (years)	56 (44, 68) [100]	62 (49, 71) [100]	54 (44, 65) [100]	55 (42, 67) [100]	0.0006~
Gender, N(%) female	397 (66) [100]	85 (53.1) [100]	180 (72.3) [100]	132 (68.4) [100]	<0.001^
Symptom duration, months	5.4 (2.9, 9.9) [100]	2.7 (2.4, 5.9) [100]	7.4 (3.8, 12.0) [100]	5.1 (2.7, 9.5) [100]	0.0001~
Swollen joint count 28	9 (4, 14) [100]	10 (5, 16) [100]	9 (4, 14) [100]	8 (4, 13) [100]	0.0243~
Swollen joint count 51	11 (6, 17) [100]	13 (6.5, 20) [100]	11 (6, 18) [100]	10 (5, 15) [100]	0.0247~
Tender joint count 28	9.5 (4, 16) [100]	10 (4, 17) [100]	8 (4, 15) [100]	10 (6, 16) [100]	0.1503~
Tender joint count 51	14 (7, 23) [100]	13 (5, 22.5) [100]	13 (6, 23) [100]	15 (9, 22) [100]	0.2272~
CRP, mg/l	8 (1, 22) [84.2]	13.5 (6.8, 38) [88.8]	8 (2, 19) [83.1]	3 (0, 11) [81.9]	0.0001~
DAS28	4.6 (3.8, 5.5) [84.2]	5.1 (4.1, 6.0) [88.8]	4.5 (3.8, 5.5) [83.1]	4.4 (3.7, 5.3) [81.9]	0.0011~
HAQ	1.00 (0.50, 1.63) [99.0]	1.25 (0.63, 1.88) [98.8]	1.00 (0.50, 1.63) [98.8]	0.88 (0.25, 1.50) [99.5]	0.0001~
Smoking status:					
Never, N(%)	177 (29.4)	42 (26.3)	80 (32.1)	55 (28.5)	0.441^
Ex, N(%)	255 (42.4)	76 (47.5)	95 (38.2)	84 (43.5)	
Current, N(%)	170 (28.2) [100]	42 (26.3) [100]	74 (29.7) [100]	54 (28.0) [100]	
RF status:					
Positive, N(%)	221 (40.3)	71 (46.4)	112 (49.8)	38 (22.4)	<0.001^
Negative, N(%)	327 (59.7) [91.0]	82 (53.6) [95.6]	113 (50.2) [90.3]	132 (77.7) [88.1]	
Anti-CCP status:					
Positive, N(%)	202 (41.1)	73 (52.5)	106 (54.6)	23 (14.6)	<0.001^
Negative, N(%)	289 (58.9) [81.6]	66 (47.5) [86.9]	88 (45.4) [77.9]	135 (85.4) [88.1]	
Current sDMARD use, N(%)	109 (18.1) [100]	75 (46.9) [100]	34 (13.7) [100]	0 (0.0) [100]	<0.001^
Time to first treatment, (months)	8.4 (4.0, 19.1) [100]	3.1 (2.0, 5.0) [100]	15.6 (10.0, 36.2) [100]	-	<0.0001~

* p values resulting from comparison of baseline score across treatment groups, ~ = Kruskal-Wallis, ^ = χ^2,
§Early treatment (ET) = treatment ≤ 6 months after symptom onset, late treatment (LT) = treatment > 6 months after symptom onset, Never treatment (NT) = patient never received DAMRDs or steroids during follow-up.
Anti-CCP = Anti-cyclic citrullinated peptide antibodies, DAS28 = Disease activity score (28), HAQ = Health assessment questionnaire, IQR = Interquartile range, l = Litres, mg = Milligrams, N = Number of patients, RA = Rheumatoid arthritis, RF = Rheumatoid factor, sDMARD = Synthetic Disease Modifying Anti-Rheumatic Drugs

Table 2 – Median 51 SJC/TJC and HAQ scores and proportion taking sDMARDs over follow-up for patients with RA, and stratified by treatment group (N=602)

					Follow-up year score, median (IQR)					
		0	1	2	3	5	7	10	15	20
SJC 51										
	Total	11 (6, 17)	3 (1, 9)	2 (0, 8)	2 (0, 7)	-	-	2 (0, 5)	1 (0, 4)	1 (0, 3)
	ET	13 (6.5, 20)	4 (1, 10)	3 (0, 8)	2.5 (0, 9)	-	-	2 (0, 6)	1 (0, 4)	0.5 (0, 2)
	LT	11 (6, 18)	4 (1, 11)	3 (1, 9)	3 (0, 9)	-	-	2 (0, 7)	1 (0, 5)	1 (0, 4)
	NT	10 (5, 15)	2 (1, 8)	1 (0, 6)	2 (0, 5)	-	-	1 (0, 3)	0.5 (0, 2)	0 (0, 2)
TJC										
	Total	14 (7, 23)	6 (2, 15)	5 (1, 15)	5 (1, 15)	-	-	3 (0, 12)	4 (0, 15)	4 (0, 12)
	ET	13 (5, 22.5)	5 (1, 15)	4 (1, 13)	4.5 (0, 14.5)	-	-	2 (0, 11)	2 (0, 12)	2.5 (0, 5)
	LT	13 (6, 23)	7 (1, 17)	7 (2, 18)	5 (2, 16.5)	-	-	4 (1, 15)	6 (1, 19.5)	6 (1, 16)
	NT	15 (9, 22)	6 (2, 14)	4 (1, 12)	4 (1, 10.5)	-	-	3 (0, 10)	3.5 (1, 12)	4 (0, 7)
HAQ										
	Total	1.00 (0.50, 1.63)	0.75 (0.25, 1.50)	0.75 (0.25, 1.63)	0.88 (0.25, 1.63)	1.00 (0.3, 1.75)	1.13 (0.5, 1.88)	1.25 (0.38, 2.00)	1.25 (0.50, 2.00)	1.38 (0.50, 2.00)
	ET	1.25 (0.63, 1.88)	0.75 (0.13, 1.56)	0.88 (0.25, 1.75)	0.88 (0.25, 1.88)	1.06 (0.38, 1.88)	1.13 (0.50, 1.88)	1.25 (0.38, 2.13)	1.38 (0.75, 2.13)	1.38 (0.81, 2.00)
	LT	1.00 (0.50, 1.63)	0.88 (0.38, 1.63)	1.00 (0.25, 1.75)	1.13 (0.38, 1.75)	1.13 (0.50, 1.88)	1.25 (0.50, 1.88)	1.50 (0.63, 2.00)	1.50 (0.63, 2.00)	1.50 (0.69, 2.13)
	NT	0.88 (0.25, 1.50)	0.50 (0.13, 1.25)	0.50 (0.13, 1.13)	0.63 (0.00, 1.25)	0.88 (0.25, 1.50)	0.88 (0.25, 1.50)	0.88 (0.25, 1.38)	1.00 (0.25, 1.75)	0.88 (0.25, 1.63)
sDMARD §										
	Total	109 (18.1)	204 (35.7)	203 (38.5)	207 (41.0)	179 (38.3)	160 (40.6)	153 (40.9)	127 (45.2)	98 (47.3)
	ET	75 (46.9)	98 (62.4)	93 (63.7)	85 (59.4)	69 (45.8)	56 (53.9)	55 (57.3)	45 (60.0)	31 (57.4)
	LT	34 (13.7)	106 (43.1)	110 (46.4)	122 (54.0)	110 (52.1)	104 (55.6)	98 (54.8)	82 (58.6)	67 (62.0)
	NT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

ET = early treatment, HAQ = Health Assessment Questionnaire, IQR = Interquartile range, LT = late treatment, N = Number, NT = never treatment, sDMARD = synthetic disease modifying anti-rheumatic drug, SJC = swollen joint count, TJC = tender joint count

§ = N(%) displayed for current sDMARD use

Table 3 – The association between early treatment and HAQ scores over 20 year, including the analysis carried out on the patients with RA and the analysis on the total IP cohort

	RA patients		Total cohort	
Treatment regime	N	β (95% CI)	N	β (95% CI)
Adjusted for age and gender				
Never prescribed treatment (NT)	193	0	442	0
Late treatment (LT)	249	0.27 (0.15, 0.39)	347	0.37 (0.28, 0.46)
Early treatment (ET)	160	0.25 (0.11, 0.38)	211	0.36 (0.26, 0.47)
Further adjusted*				
Never prescribed treatment (NT)	193	0	442	0
Late treatment (LT)	249	0.10 (0.02, 0.17)	347	0.11 (0.06, 0.17)
Early treatment (ET)	160	0.03 (-0.06, 0.12)	211	0.04 (-0.03, 0.11)

* Models adjusted for: baseline gender, ACPA, RF, RA, smoking status, HAQ, SJC, TJC, CRP; time-varying age, CRP, SJC, TJC and comorbidities and weighted using inverse probability of treatment / censoring weights

FIGURE LEGENDS

Figure 1 – Survival curves of the three treatment groups (patients with RA only) after adjusting for age and gender

Figure 2 – Median HAQ score at each follow-up, (a) patients with RA, (b) total IP cohort
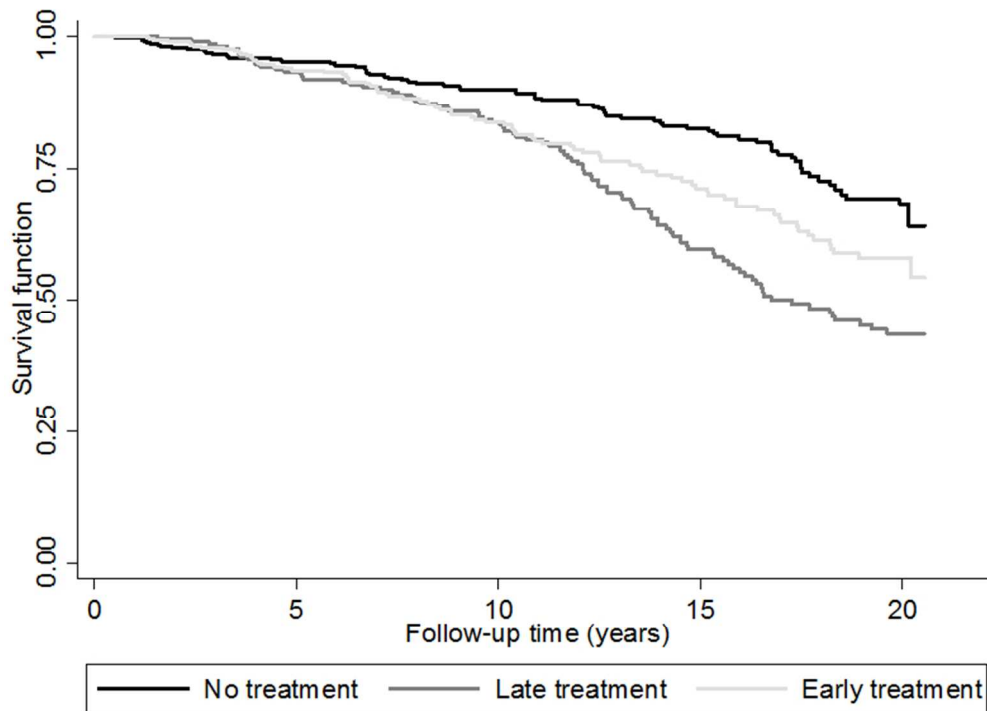
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Figure 1 – Survival curves of the three treatment groups (patients with RA only) after adjusting for age and gender
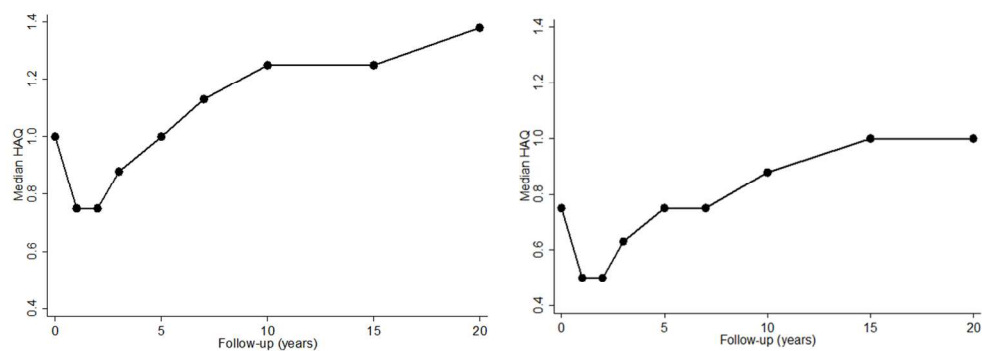Figure 1
66x49mm (300 x 300 DPI)

Figure 2 – Median HAQ score at each follow-up, (a) patients with RA, (b) total IP cohort
Figure 2
110x44mm (300 x 300 DPI)