EXTENDED REPORT

Early remission is associated with improved survival in patients with inflammatory polyarthritis: results from the Norfolk Arthritis Register

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ABSTRACT

Objectives This study aimed to evaluate whether the early achievement of clinical remission influences overall survival in an inception cohort of patients with inflammatory polyarthritis (IP).

Methods Consecutive early IP patients, recruited to a primary care based inception cohort from 1990 to 1994 and from 2000 to 2004 were eligible for this study. Remission was defined as absence of clinically detectable joint inflammation on a 51-joint count. In sensitivity analyses, less stringent definitions of remission were used, based on 28-joint counts. Remission was assessed at 1, 2 and 3 years after baseline. All patients were flagged with the national death register. Censoring was set at 1 May 2011. The effect of remission on mortality was analysed using the Cox proportional hazard regression model, and presented as HRs and 95% CIs.

Results A total of 1251 patients were included in the analyses. Having been in remission at least once within the first 3 years of follow-up was associated with a significantly lower risk of death: HR 0.72 (95% CI 0.55 to 0.94). Patients who were in remission 1 year after the baseline assessments and had persistent remission over time had the greatest reduction in mortality risk compared with patients who never achieved remission within the first 3 years of follow-up: HR 0.58 (95% CI 0.37 to 0.91). Remission according to less stringent definitions was associated with progressively lower protective effect.

Conclusions Early and sustained remission is associated with decreased all-cause mortality in patients with IP. This result supports clinical remission as the target in the management of IP.

INTRODUCTION

Patients with inflammatory polyarthritis (IP), and its subset rheumatoid arthritis (RA), have an increased mortality risk compared with the general population.[1] For this reason, mortality should be regarded as one of the most important long-term outcomes of the management of IP.

Within RA cohorts, predictive markers for mortality include: sociodemographic variables (age, gender, education level); non-modifiable disease variables (disease duration, comorbidities, rheumatoid factor (RF), anticitrullinated protein antibody, extra-articular disease); and potentially modifiable variables including functional disability and measures of disease activity particularly the swollen joint count.[1–5] Acute phase reactants, including both erythrocyte sedimentation rate and C reactive protein (CRP), have also been strongly linked to increased risk of death, mainly from cardiovascular causes.[2 6–9] Also composite disease activity indexes, both at baseline and cumulatively, have consistently been found to be associated with increased risk of death in longitudinal cohorts of RA.[9–11] Cut-offs around low disease activity have been identified as relevant predictors of mortality in these studies.

In this context, achieving remission is regarded as the most desirable outcome in IP, including RA.[12] This is based on strong evidence in terms of better structural and functional outcomes.[13–15] Such results are highly consistent throughout the literature, despite quite different definitions of remission being applied.[14] Although recently a new definition of remission was proposed, a fully valid definition of remission for RA is still not available, even though the most stringent ones seem to be better in terms of predicting long-term outcomes.[16 17] Given that increased mortality is the most important long-term consequence of RA,[1 18] the hypothesis that inducing remission from the earliest phases of the disease could mitigate this higher risk of death is highly relevant. Long-term large observational studies are currently the most feasible study design in which to address this question.

A recent multi-centre cohort study including 704 early RA patients explored the influence of sustained remission, measured by the Disease Activity Score (DAS),[19] on all-cause mortality.[15] Although, out of 78 patients who had sustained remission, a 32% relative decrease in mortality risk of death was observed, the study was underpowered to find a significant association. Therefore, the question whether early achievement of a status of clinical remission might be associated with a significant decrease is still to be answered.

The Norfolk Arthritis Register (NOAR) is a unique inception cohort of patients with early IP who are followed longitudinally using standardised protocols.[20] We sought to investigate the association between early remission according to different definitions with overall survival within the NOAR cohort.

METHODS

Study design, setting and participants

Since 1990, patients with early IP have been recruited to NOAR, a large primary care based inception cohort in the east of the UK. A detailed

description of this register has been reported elsewhere.[20] Briefly, consecutive cases of IP are notified through general practitioners or attendance at hospital rheumatology clinics within this catchment area. The notification criteria are adults aged ≥16 years at symptom onset, swelling of ≥2 joints persisting for ≥4 weeks. For the present study, we only included patients recruited between 1990 and 1994 and between 2000 and 2004 because these two groups of patients were clinically assessed at baseline, 1, 2 and 3 years after inclusion to the register. Only patients with symptom duration of less than 2 years at baseline visit, who were still alive at the time of the third assessment, were eligible for this analysis. This last inclusion criterion was chosen in order to have the opportunity to evaluate the timing and persistency of remission on mortality. This study was conducted with the approval of the Norfolk and Norwich University Hospital Local Research Ethics Committee. All subjects gave written consent.

Demographic and clinical assessments

At baseline, patients were assessed by a research nurse using a structured interview and clinical examination. Baseline data included age, gender, date of symptom onset and smoking status (current, ex- and never). The American College of Rheumatology (ACR) 1987 criteria for RA were applied at baseline and cumulatively.[21] Baseline and follow-up clinical assessments included the number of swollen and tender joints (based on 51-joint count).[22] The British version of the Health Assessment Questionnaire (HAQ) was completed by the patients at baseline and annually thereafter.[23] Blood samples were taken and frozen to determine RF (latex test), anticitrullinated protein antibody status (Axis-Shield Diastat Anti-CCP kit, Dundee, Scotland) and CRP levels at a later stage.[24 25] The 28-joint DAS (DAS28-3-CRP)[26] was then calculated. Use of disease modifying antirheumatic drugs (DMARDs) and/or oral corticosteroids, including start and stop date, were also collected at each follow-up visit. Remission was defined according to three predefined definitions, as previously reported.[14] All the remission definitions and variables are summarised in table 1. All patients were flagged with the Office for National Statistics and followed up from the date of symptom onset to date of death, embarkation date or 1 May 2011, whichever came first. Patients who no longer could be tracked because they moved out of the country (n=5; 0.004%) were censored on the date of 'embarkation.'

Statistical analysis

Primary analysis consisted of investigating the association between the first definition of remission and all-cause mortality. The following individual remission states were tested as independent variables: (1) 'remission ever'; (2) 'remission score'; and (3) 'time to remission' in separate Cox proportional hazard regression models. All models were adjusted for age and gender. The same analyses were repeated adjusting for other variables that were recognised as potential confounders from the literature,[1] coded as follows: current smoker at baseline; RF (≥1:40); symptom duration at baseline; number of swollen joints at baseline (quartiles); CRP levels at baseline (quartiles); HAQ score (quartiles); and year of registration. The influence of the following treatment variables was also evaluated: previous and/or concurrent treatment with DMARDs (dichotomous); DMARD duration (tertiles); and concurrent steroids (dichotomous).

Since remission score and time to first remission are linked (eg, only patients who achieve remission at the initial assessment can have all visits in remission), we also analysed the interaction between these two variables. The interacting variable identified six levels of progressively higher exposure to remission (increasing number/decreasing timing): remission once at year 1, 2 and 3, remission twice with first remission at year 1 or 2 and three times in remission. In secondary analysis, similar models were fitted for remission definitions 2 and 3. Effect modification was systematically explored by fitting interactions between remission variables and confounders in multivariable models. Proportional hazard assumption was tested by formal tests on Shoenfield residuals. Results are presented as HRs and 95% CIs. Missing data on confounders were imputed using switching regression, an iterative multivariable regression technique which retains an element of random variation in the estimates.[27] The available sample size and number of events were able to detect an HR of approximately 0.75 with a power of 80% and α=0.05. All analyses were conducted using Stata V.11 (StataCorp, College Station, Texas, USA).

Table 1 Definitions of clinical remission

Remission 1	Swollen joint count on 51+tender joint count on 51=0
Remission 2	Swollen joint count on 28+tender joint count on 28=0
Remission 3	Swollen joint count on 28≤1 and tender joint count on 28≤1
Ever remission	At least one assessment in remission at year 1, 2 or 3
Remission score	Number of assessments in remission at year 1, 2 or 3
Time to remission	Year of the first assessment in remission within the first 3 years

51-joint count: neck, shoulders, elbows, wrists, hips, knees, the 10 metacarpophalangeal joints, the 10 proximal and 10 distal interphalangeal joints of the hands, and the 10 metatarsophalangeal joints of the feet.
28-joint count: shoulders, elbows, wrists, knees, the 10 metacarpophalangeal joints, and the 10 proximal interphalangeal joints of the hands.

RESULTS

Out of a total of 1404 subjects eligible, 1251 subjects (89.1%) with complete joint count data at each time point were included in this analysis. Baseline demographic and clinical disease characteristics of the study sample are summarised in table 2. Median age at inclusion in the cohort was 57.1 years (IQR 46.6–68.5), with two-thirds being women. The median duration of symptoms at registration was 5.7 months (IQR 3.1–10.1). At the baseline assessment, 48.8% were classified as having RA according to 1987 ACR classification criteria. By the third year anniversary, 73.1% of patients had fulfilled the ACR criteria and 57.8% had been treated with a DMARD.

In the years from registration to the starting time of this study (third anniversary), 384/1251 patients (30.7%) were classified in remission according to definition 1, of whom 57%, 25% and 18% achieved the first remission at year 1, 2 and 3, respectively (table 3). As expected, less stringent definitions led to increasing occurrence of remission, ranging from 30.7% of patients achieving remission at least once during the first 3 years according to definition 1 to 54.1% according to definition 3 (see online supplementary table S1).

Due to missing data on several confounders for the adjusted analyses, the number of subjects with complete available data was 961 (68.4%). Using multiple imputation (20 datasets) of remission variables and confounders, 1251 subjects were available for all the adjusted analyses.

Starting from the third year of observation, over a median follow-up of 7.93 years (IQR 4.7–14.8), corresponding to 12 030 person-years, 348/1251 (26.5%) deaths occurred.

Table 2 Baseline demographic and disease characteristics of the study sample

Variable	Value
N	1251
Age at registration (years): median (IQR)	57.1 (46.6, 68.4)
Female: no. (%)	820 (65.5)
Symptoms duration (months): median (IQR)	5.7 (3.1, 10.1)
Current smoker at registration: no. (%)	307 (26.6)
Satisfied 1987 ACR criteria for RA at registration: no. (%)	611 (48.8)
RF positive: no. (%)*	367 (32.9)
Presence of nodules: no. (%)	93 (7.4)
Shared epitope (1/2 alleles): no. (%)†	517 (47.1)/158 (14.4)
Swollen joint count out of 51: median (IQR)	5 (2, 12)
Tender joint count out of 51: median (IQR)	6 (2, 16)
Swollen joint count out of 28: median (IQR)	4 (1, 10)
Tender joint count out of 28: median (IQR)	4 (1, 11)
CRP (mg/l): median (IQR)‡	7.1 (2, 20)
DAS28–CRP (3): median (IQR)‡	3.9 (2.9, 4.9)
HAQ score: median (IQR)	0.9 (0.4, 1.5)

*RF factor measured on 1114 subjects.
†Shared epitope measured on 1097 subjects.
‡CRP measured on 1042 subjects.
ACR, American college of rheumatology; CRP, C reactive protein; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor.

Primary analyses

Subjects who had experienced at least one period of remission according to definition 1 within the first 3 years of follow-up showed a 27% relative reduction in the risk of all-cause mortality (HR 0.73 (95% CI 0.56 to 0.94)). This reduction was still around 28% after adjusting for all confounders (adjHR 0.72 (95% CI 0.55 to 0.94)) (table 4 and see online supplementary table S2). Further adjustment for DMARDs duration and steroid use did not modify the estimated HR for remission (0.73 (95% CI 0.56 to 0.95)).

No statistically significant interactions were found between remission variables and confounders: age, gender, smoking status, swollen joints at baseline, symptom duration, HAQ, CRP, RF, presence of nodules and year of registration/cohort. Restricted analyses to subgroups of patients showed a slightly higher reduction of the risk of death associated with remission in men, in patients fulfilling 1987 ACR criteria or ever treated with DMARDs (see online supplementary table S2).

Table 3 Occurrence of clinical remission within the first 3 years of follow-up

	Remission 1
Remission ever, n (%)	384 (30.7)
Remission score, n (%)	
1	220 (17.6)
2	95 (7.6)
3	69 (5.5)
Time to first remission, n (%)	
1st year	168 (13.4)
2nd year	118 (9.4)
3rd year	98 (7.8)

Evaluated on complete data on remission of 1251 subjects.

Table 4 Effect of remission according to different definitions of remission on all-cause mortality

	Remission 1	
	HR (95% CI)*	HR (95% CI)†
Ever in remission	0.73 (0.56 to 0.94)	0.72 (0.55 to 0.94)
Remission score	0.86 (0.74 to 0.99)	0.85 (0.73 to 0.99)
Time to first remission		
1 year	0.68 (0.46 to 0.98)	0.65 (0.60 to 0.71)
2 years	0.61 (0.40 to 0.91)	0.56 (0.51 to 0.61)
3 years	0.95 (0.65 to 1.40)	1.03 (0.95 to 1.12)

Remission 1: swollen joint count on 51+tender joint count on 51=0.
*Adjusted for age and gender.
†Adjusted for age, gender, smoke, RF, previous and/or concurrent treatment with DMARDs, symptoms duration at baseline, swollen joints at baseline, CRP levels at baseline, HAQ at baseline and calendar year; based on multiple imputation of missing data.
CRP, C reactive protein; DMARD, disease modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor.

The number of assessments in remission (remission score) was associated with a proportional decrease of the mortality risk (HR 0.86(95% CI 0.74 to 0.99)), even after adjusting for confounders (adjHR 0.85 (0.73 to 0.99)).

The time to first remission was associated with a decreased risk of death. The lowest risks of death were observed if the patient's first documented remission occurred at either the first or second anniversary after registration (HR 0.68 (95% CI 0.46 to 0.98) and 0.61 (95% CI 0.40 to 0.91), respectively), compared with subjects who did not achieve remission ever, even after adjusting for confounders (adjHR 0.65 (95% CI 0.60 to 0.71) and 0.56 (95% CI 0.51 to 0.61), respectively). When first remission was not achieved until the third anniversary, no significant advantage in survival was noted (adjHR 1.03 (95% CI 0.95 to 1.12)).

The interacting variable between time to first remission and remission score showed that, for each additional level of exposure to remission (increasing number/decreasing timing), a mean decrease of about 10% of risk of mortality was observed (adjHR 0.91 (95% CI 0.84 to 0.98)).

The lowest risk of death was observed for patients with the maximum number of times in remission (adjHR 0.58 (95% CI 0.37 to 0.91)).

Secondary analyses

In order to verify the relevance of a stricter definition of remission on mortality, we tested and compared the effect of two other definitions which were progressively more permissive in terms of residual joint involvement (see online supplementary table S2). Clinical remission according to definitions 1 and 2 showed similar strength of association with mortality, while the more permissive criterion did not show statistically significant association to the outcome (adjHR 0.82 (95% CI 0.64 to 1.03)).

Since less stringent criteria also included subjects fulfilling more stringent criteria, we used contrasts to separate the single effect of each definition (table 5). Overall, only subjects in remission according to the most stringent criterion (definition 1) showed a significant decreased risk of mortality (adjHR 0.71 (95% CI 0.53 to 0.94)), while mortality was not significantly decreased in patients in remission only according to definition 2 or 3.

Table 5 Specific effect of remission according to different definitions of remission on all-cause mortality

Remission 1 Sw 51+Tn51=0	Remission 2 Sw28+Tn28=0	Remission 3 Sw28≤1 and Tn28≤1	All-cause mortality HR (95% CI)*	All-cause mortality HR (95% CI)†
–	–	–	1	1
–	–	✓	0.95 (0.70 to 1.29)	1.01 (0.74 to 1.38)
–	✓	✓	0.80 (0.52 to 1.23)	0.81 (0.52 to 1.27)
✓	✓	✓	0.70 (0.53 to 0.92)	0.71 (0.53 to 0.94)

*Adjusted for age and gender.
†Adjusted for age, gender, smoke, RF, previous and/or concurrent treatment with DMARDs, symptoms duration at baseline, swollen joints at baseline, CRP levels at baseline, HAQ at baseline and calendar year; based on multiple imputation of missing data.
CRP, C reactive protein; DMARD, disease modifying antirheumatic drug, HAQ, Health Assessment Questionnaire; RF, rheumatoid factor; Sw, swollen joint count; Tn, tender joint count.

DISCUSSION

This study sought to determine the predictive value of a pragmatic definition of remission on all-cause mortality in a primary care based inception cohort of patients with IP. This is the largest study to investigate this relationship. The particular setting of NOAR allowed us to measure the effect of remission, taking into account several potential confounders, thus providing more precise and less biased measures of association.

In this study we included two groups of patients, recruited 10 years apart. Differences between these two groups have been previously reported.[14] The second group comprised patients with longer mean symptom duration, higher disease activity, higher disability, but, probably due to a more intensive treatment strategy, a higher proportion of patients from the second group achieved a status of clinical remission. Given that belonging to a specific group did not modify the effect of remission variables, we analysed the two groups together, adjusting for year of registration, as well as for other confounders, in order to increase the power of our analyses.

We found that the achievement of remission within the first 3 years from the diagnosis was associated with a fall of about 30% in the risk of all-cause mortality thereafter.

Among subjects in clinical remission within the first 3 years there were subjects who fulfilled the criteria of remission only once and subjects who were in remission on two or three annual follow-up visits. The increasing number of times spent in remission showed an incremental effect on mortality. A recent study investigated the effect of sustained clinical remission (3, 4 and 5 years after inclusion in an inception cohort) according to DAS remission criteria on mortality in 704 patients with early RA. The authors reported a mortality of 15.4% of death in the sustained remission group (78 patients) and a 22.6% in patients without sustained remission, corresponding to a risk ratio of 0.67 (95% CI 0.39 to 1.16).[15] Despite the lack of power of this study, mainly due to the low number of events in the remission group, these data support a tendency toward a better outcome in patients with a persistent status of remission, as our data show.

With regard to the time to first remission, we found that the subgroup of patients who were in remission within the first 2 years after inclusion showed the lowest risk of mortality compared with those who never achieved remission within the first 3 years of observation. This is in keeping with other published studies suggesting that early response is associated with a lower mortality risk, as well as a lower risk of other relevant long-term outcomes including joint damage and disability.[28–31]

Given that the number of times spent in remission and time to remission are strictly related, these results should be interpreted together. Interacting these two variables we found that the lowest risk of death was associated with the earliest and most persistent status of remission. This might be due to the overall exposure to active inflammatory process, which is regarded as the main cause of premature mortality in IP.[6–9] This result is consistent with previous studies which reported a significant lower mortality risk in patients with cumulative lower disease activity (DAS28<3.7).[11]

The influence of remission was still significant even after controlling for several variables which may affect both the probability of being in remission and the risk of dying, including age, gender, smoking status, RF, baseline HAQ and disease activity variables, fulfilment of RA classification criteria and treatment. Furthermore, fully adjusted estimates did not significantly differ from age- and gender-adjusted ones, indicating an independent association between remission and survival, which could be explained by residual confounding due to our substantial inability to predict response in IP.[32]

Among adjusting variables, effect modifiers have been previously described. In NOAR, excess mortality was confined to patients who were RF positive.[33] Also, the effect of high DAS28 on mortality was slightly higher in men (HR 1.58) than in women (HR 1.21).[11] We systematically investigated the possible interaction between remission and other variables. Given that RF was not associated to remission, RF did not modify the effect of remission on mortality in this analysis. Though no significant statistical interactions were found, the protective effect of remission was slightly higher in men, as previously reported in RA.[34 35]

Remission in DMARD treated patients was associated with an even better outcome, supporting that treatment-induced remission may influence survival rather than natural remission.[28 36] In our analyses, we also confirmed the well established independent association of age, gender, HAQ, CRP, presence of nodules and steroid treatment with mortality.

We explored the impact of different definitions of remission which were more permissive in terms of residual joint inflammation. Investigating the specific association of each definition of remission, we found that the greatest weight was due to the fulfilment of the most stringent definition. This result is in accordance with the current belief that more stringent criteria for remission could identify a more robust status of complete disease control compared with more permissive criteria (eg, DAS28).[16 17 37 38]

This study has some limitations. Due to the study design, we were not able to apply any of the current definitions of remission (neither dimensional criteria based on specified cut-offs of continuous DASs nor categorical criteria based on fulfilment of prespecified items).[37 39] Our definitions, only based on swollen and tender joint count, clearly lack content validity, since they exclude acute phase reactants and patient's or assessor's

reported measures. Nevertheless, as already demonstrated against functional disability, this lack of complete content validity does not affect the predictive validity of our definitions of remission.[14] Given that acute phase reactants, as single measures of disease activity, have been consistently associated with worse survival rate, we could speculate that remission definitions including CRP could improve the predictive validity of remission still further. On the other hand, these results indicate that a soft predictor such as a simple clinically based definition of remission is still able to discriminate between patients with different hard outcomes such as mortality.

In summary, this study demonstrates that achieving remission early in the disease course of IP, even according to a simple clinically based definition, is associated with better survival. This result gives a further piece of evidence supporting the use of remission as a relevant outcome target in clinical practice, suggesting that achieving this target early in the disease course may change the fate of the disease even in terms of long term outcomes such as premature death.

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