Improved treatment strategies reduce the increased mortality risk in early RA patients

Jessica A. B. van Nies¹, Zuzana de Jong¹, Annette H. M. van der Helm-van Mil¹, Rachel Knevel¹, Saskia Le Cessie² and Tom W. J. Huizinga¹

Abstract
Objective. A higher mortality rate in patients with RA than in the general population has been reported in most series. Treatment strategies for RA have improved dramatically over the last decades, resulting in less inflammation and joint damage. We investigated whether this change in treatment corresponds to reversal of excess mortality by studying a large inception cohort of early RA patients exposed to different treatment strategies.

Methods. Six hundred and eighty-four RA patients included in the Leiden Early Arthritis Clinic between 1993 and 2008 were studied. Treatment was different for three inclusion periods. From 1993 to 1995 patients were treated with NSAIDs and only late in their disease with DMARDs. From 1996 to 1998 patients were promptly treated with HCQ or SSZ. From 1999 to 2008 patients were immediately treated with MTX monotherapy or in combination with other disease-modifying drugs. Life/death status was tracked nationally using the civic registries. Mortality rates were compared with the general Dutch population.

Results. In Periods 1 and 2, increased standardized mortality rates were found, 1.35 (95% CI 0.94, 1.93) and 1.23 (95% CI 0.91, 1.67), respectively, while a decreased standardized mortality rate was found for patients included in 1999–2006 [0.49 (95% CI 0.31, 0.77)]. Age of onset [hazard ratio (HR) 1.10 (95% CI 1.07, 1.13)], erosive disease [HR 2.03 (95% CI 1.22, 3.37)], high CRP level [HR 1.09 (95% CI 1.01, 1.18)], smoking [HR 2.39 (95% CI 1.31, 4.38)] and higher baseline HAQ score [HR 1.53 (95% CI 1.06, 2.20)] associated with mortality.

Conclusion. Current treatment strategies for early RA, such as that given in inclusion Period 3, might contribute to the reversal of excess mortality in RA.

Key words: Mortality, Survival, Rheumatoid arthritis, Inception cohort, Treatment strategies.

Introduction
RA is a chronic inflammatory disease that is characterized by polyarthritis joint damage, disability and decreased work participation [1]. A recent review showed that mortality rates in RA are 1.5- to 1.6-fold higher than in the general population; this was based on 84 unique cohorts [2]. The attributed causes of death are similar to the general population with cardiovascular diseases being the primary cause of death [2, 3]. Patient or disease characteristics that are associated with a severe course of RA were found associated with higher risks of death [2].

In the past 20 years, treatment strategies for RA have dramatically changed. Prompt start of DMARDs, combination therapy and tight control of disease activity are currently proved to be essential for beneficial disease outcome [4–6]. Treatment strategies composed of these three components are more effective in achieving remission and preventing joint damage [7]. Since the increased mortality risk is associated with other severity outcomes such as joint damage and since levels of joint destruction are reduced by the improved treatment strategies, we hypothesized that mortality rates benefit from these treatment strategies as well. This hypothesis is supported by observational studies on RA patients treated with MTX.
and anti-TNF, which showed improved survival [8–10]. However, whether nowadays treatment strategies indeed reduce the increased mortality risk is thus far unknown.

Therefore, the present study aimed to investigate whether changes in treatment strategies are also reflected by changes in mortality rates. For this we took advantage of a unique longitudinal cohort of early RA patients that includes patients since 1993 and in which treatment strategies have changed dramatically over time. From 1993 till 1995 a wait-and-see policy applied and initial MTX was almost never used. From 1996 till 1998 treatment with HCQ or SSZ was initiated immediately but initial MTX was infrequently prescribed. From 1999 onwards, however, immediate treatment with MTX or combination therapy was initiated.

**Methods**

**Study design**

The Leiden Early Arthritis Clinic (EAC) is a clinical inception cohort consisting of patients with recent-onset arthritis referred to the Department of Rheumatology of the Leiden University Medical Center (LUMC) from 1993 and onwards [11]. Patients were included when arthritis was observed by a rheumatologist. At the time of analysis, April 2008, the EAC consisted of 2079 patients with recent-onset arthritis (no longer than 2 years) of any origin. Written informed consent was obtained from all participants. The study was approved by the appropriate local institutional review board (Ethische Commissie van het LUMC). For this study we selected the patients who fulfilled, within 1 year of follow-up, the ACR 1987 revised criteria for RA (n = 684) [12]. In order to investigate whether treatment influenced the survival of RA patients, patients were divided into three separate inclusion periods in which different treatment strategies were applied. The first inclusion period concerns 1993–95. The 108 RA patients included in this period were treated initially with NSAIDs and subsequently with chloroquine or SSZ if they had persistent active disease. The decision to start with, the dosage and the choice of DMARD were left to the treating rheumatologist’s discretion. In the second inclusion period, 1996–98, 174 RA patients were routinely treated with NSAIDs and promptly treated with either chloroquine or SSZ [13]. In the third period (inclusion between 1999 and 2006), the majority of the 402 RA patients were promptly treated with MTX monotherapy and a minority with monotherapy of other DMARDs or initial combination therapy (Table 1). In all three inclusion periods, an equal number of patients received biological agents somewhere during the follow-up period. Moreover, in 2000, treatment adjustments based on DASs were introduced.

**Patient assessments**

At inclusion, a physical examination was performed and smoking history was taken. Patients filled in a HAQ, modified for use in Dutch patients [14]. Radiographs of hands and feet were made and scored by experienced readers, using the Sharp–van der Heijde method [15]. Blood samples were taken to determine ESR, CRP and IgM RF (ELISA) and CCP status (ELISA) (Immunoscan RA, MARK 2; Euro-Diagnostica, Arnhem, The Netherlands). Anti-CCP positivity had a cut-off level of 25 arbitrary units.

**Notification of death**

Patients were followed longitudinally from the moment of their inclusion in the EAC cohort until 1 April 2008 or until their death. All patients were tracked nationally using the civic registries (Gemeentelijke Basis Administratie, GBA) to ascertain life/death status. Mortality data of the general Dutch population were obtained from Statistics Netherlands [16].

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**Table 1** Differences in treatment strategy for the three inclusion periods

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<tr>
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<tbody>
<tr>
<td><strong>Initial monotherapy, %</strong></td>
<td></td>
<td></td>
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<tr>
<td>HCQ</td>
<td>50</td>
<td>29.5</td>
<td>15.2</td>
</tr>
<tr>
<td>SSZ</td>
<td>40</td>
<td>61.0</td>
<td>14.5</td>
</tr>
<tr>
<td>MTX</td>
<td>5</td>
<td>9.5</td>
<td>70.3</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td><strong>Initial combination therapy, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX + SSZ</td>
<td>1.5</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>MTX + SSZ + HCQ</td>
<td>1.5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td><strong>Initial combination therapy with oral prednisone</strong></td>
<td></td>
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<tr>
<td>Delay in treatment initiation, median (interquartile range 25–75)</td>
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<tr>
<td>Time between symptom onset and inclusion, months</td>
<td>9.9 (6.3–18.5)</td>
<td>6.1 (3.0–10.8)</td>
<td>6.0* (2.8–10.0)</td>
</tr>
<tr>
<td>Time between symptom onset and start of DMARD therapy, months</td>
<td>5.1 (2.6–10.7)</td>
<td>4.2 (2.2–6.9)</td>
<td>4.2 (2.4–8.6)</td>
</tr>
<tr>
<td>Time between inclusion in EAC and start of DMARD therapy, days</td>
<td>107 (48.5–227.5)</td>
<td>20 (14–56)</td>
<td>27* (9–60)</td>
</tr>
</tbody>
</table>

None of the patients was initially treated with anti-TNF. During the available follow-up the frequency of anti-TNF use was not different between the three groups (2.8, 4.6 and 4.2%, respectively). *P < 0.0001.
Analysis of data

Differences in characteristics at inclusion were compared with the t-test and one-way ANOVA for continuous variables and the chi-square test for nominal variables. Data are expressed as mean (s.d.) with a 95% CI, unless otherwise stated. The mortality of RA patients is compared with the general population using standardized mortality ratios (SMRs). SMR is the ratio between the observed number of deaths of RA patients and the expected number of deaths in the general Dutch population adjusted for age, sex and inclusion period. Analyses were done stratified by inclusion period and for each inclusion year compared with the general Dutch population. Survival curves were calculated using Kaplan–Meier survival curves. Expected survival curves of the Dutch population were calculated using the methods of Hakulinen [17]. This method is based on the concept of an expected life table and takes differences in patient withdrawal of subgroups of patients with equal relative survival rates into account.

Associations between risk factors for RA severity and survival were studied using univariate and multivariate Cox proportional hazards and regression models. All studied variables were entered in the multivariate model because the P-value in the univariate model can be falsely high or low if there are confounding effects. A number of patients had missing values for some of the variables [BMI (n = 253), RF (n = 22), anti-CCP (n = 168), erosions (n = 197), ESR (n = 28), CRP (n = 59), smoking (n = 79), HAQ (n = 131)], which would have resulted in their exclusion from the multivariate model. For these patients we used multivariate imputation by chained equations to obtain five imputed data sets [18] and the results of the analyses of the five imputed data sets were pooled to obtain the correct s.e.s of the estimates [19]. Cox regression analyses were done with and without the imputed data.

All statistical analyses were performed by using Statistical Package for Social Sciences version 14.0 (SPSS, Chicago, IL, USA), STATA 11 was used to calculate the SMRs and expected survival curves and R was used to perform the multiple imputations [20]. In all tests, P < 0.05 was considered to be statistically significant.

Results

Baseline characteristics

In total, 684 RA patients were included between 1 January 1993 and April 2006. Baseline characteristics of all RA patients as well as for the patients in the three inclusion periods are presented in Table 2. The delay between the first onset of symptoms and assessment by the rheumatologist was not significantly different in all three time periods, indicating a comparable referral strategy by the general practitioner in all treatment periods. In contrast, the patients included in the second and third inclusion periods had less delay in initiation of DMARDs after assessment by the rheumatologist compared with patients included in the first period.

SMRs

During follow-up 90 RA patients died, while 85 deaths were expected within the general population. Mean age at death was 75.8 (s.d. 9.6) years. No difference in mortality was observed between all included RA patients [SMR 0.95 (95% CI 0.78, 1.17)] and the matched general Dutch population. Male RA patients had an SMR of 0.87 (95% CI 0.63, 1.21) and female RA patients an SMR of 1.02 (95% CI 0.78, 1.33). Subsequently the SMRs for the three inclusion periods were determined (Fig. 1A–C). An increased mortality rate was found in Period 1 as well as in Period 2 [SMR 1.35 (95% CI 0.95, 1.93) and SMR 1.23 (95% CI 0.91, 1.67), respectively]. In contrast, a decrease in mortality rate was found in patients included from 1999 until 2006 [SMR 0.49 (95% CI 0.31, 0.77)]. The SMRs in the three inclusion periods were statistically significantly different (P = 0.0002), and together these data reveal a nullification of the increased mortality risk. The log rank test of the three inclusion periods had a P = 0.008.
Risk factors associated with mortality
In the univariate analysis, all analysed factors were associated with increased risk of mortality in our RA population except for BMI, RF, anti-CCP and smoking status (Table 3). The multivariate analysis revealed that a higher age [hazard ratio (HR) 1.10 (95% CI 1.07, 1.13)], the presence of erosive disease [HR 2.03 (95% CI 1.22, 3.37)], a higher CRP level [HR 1.09 (95% CI 1.01, 1.18)], smoking status [HR 2.39 (95% CI 1.31, 4.38)] as well as a higher HAQ-score [HR 1.53 (95% CI 1.06, 2.20)] at baseline were all independently associated with increased mortality. In the multivariate analysis, the inclusion period remained independently associated with mortality risk [HR 0.84 (95% CI 0.77, 0.92)] over time. As a sensitivity analysis, the multivariate analysis was performed with and without imputed data, revealing no differences (data not shown).

Discussion
The outcome of RA patients has improved over the last decade. This improvement is generally expressed by

![Graph showing survival probability over time for different inclusion periods: 1993–95, 1996–98, and 1999–2006.](https://example.com/fig1.png)
lower rates of joint destruction and higher remission rates. The findings of this study suggest that current treatment strategies might have positive impact on the survival of RA patients as well.

The relationship between therapies and mortality rates in patients with RA has been studied extensively; however, no consistent effects have been shown [2]. Importantly, to our knowledge no previous studies have investigated the relationship between different treatment strategies and mortality in an early arthritis cohort. In the present study, three treatment strategies were applied that differed importantly with regard to readiness to initiate DMARD therapy, choice of DMARDs and frequency of combination therapy (Table 1). The duration between first symptoms and first assessment by the rheumatologist was not different between the three periods, indicating that the observed findings were not thanks to early referral.

The present study not only observed reduction in the increased mortality risk in RA but also revealed a tendency towards a reduced mortality risk for patients included in the third period. At first glance, this reduced mortality rate is surprising. Apart from a higher ESR (observed in inclusion Period 1), no other differences in baseline characteristics between patients included in the three inclusion periods were found. This makes it unlikely that less severe patients were included in the third inclusion period. Another possible explanation is that patients with a serious, potentially fatal illness who also develop joint complaints will not be referred to the rheumatologist and as such contribute to the mortality rate of the general population but not of the arthritis population. At present, insufficient data are available to explore these potential explanations.

As mentioned before, this study observed a lack of increased mortality in the most recent cohort. Unfortunately, this last cohort is too small to allow a subanalysis in responders to therapy vs non-responders. So in theory it may be possible that there still is an increased mortality in the subgroup of patients who did not respond well. However, we are underpowered to make this analysis.

In line with the previous studies it was observed that a higher age at disease onset, erosive disease, a higher CRP level, smoking status and a higher HAQ-score at baseline are risk factors for mortality. Of these, erosive disease and HAQ-score are the two significant predictors of mortality (HR 2.03 and 1.53, respectively) in the univariate as well as the multivariate analysis. Smoking status was not associated with increased risk in the univariate model, though an association was found in the multivariate model. Our male patients tend to smoke more often than females and we hypothesize that this seemingly unexpected finding is due to the fact that we present HRs after adjustment for sex. Increased CRP level has previously been shown to be risk factors for mortality. Of these, erosive disease and cardiovascular mortality in particular. This suggests a link between ongoing inflammation and increased risk of cardiovascular disease.

### Table 3

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate model HR (95% CI)</th>
<th>P-value</th>
<th>Multivariate model HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.09 (1.07, 1.11)</td>
<td>&lt;0.0001</td>
<td>1.10 (1.07, 1.13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender, male</td>
<td>1.54 (1.01, 2.34)</td>
<td>0.045</td>
<td>0.85 (0.50, 1.46)</td>
<td>0.554</td>
</tr>
<tr>
<td>BMI</td>
<td>1.00 (0.94, 1.07)</td>
<td>0.906</td>
<td>0.96 (0.88, 1.05)</td>
<td>0.363</td>
</tr>
<tr>
<td>RF positive</td>
<td>1.36 (0.89, 2.10)</td>
<td>0.234</td>
<td>1.23 (0.65, 2.35)</td>
<td>0.522</td>
</tr>
<tr>
<td>Anti-CCP positive</td>
<td>1.14 (0.75, 1.76)</td>
<td>0.527</td>
<td>1.41 (0.75, 2.68)</td>
<td>0.289</td>
</tr>
<tr>
<td>Erosive disease positive</td>
<td>3.41 (2.21, 5.26)</td>
<td>&lt;0.0001</td>
<td>2.03 (1.22, 3.37)</td>
<td>0.006</td>
</tr>
<tr>
<td>ESR, first hour, mm</td>
<td>1.011 (1.006, 1.016)</td>
<td>&lt;0.0001</td>
<td>0.990 (0.980, 1.001)</td>
<td>0.085</td>
</tr>
<tr>
<td>CRP, 10 mg/l</td>
<td>1.09 (1.05, 1.14)</td>
<td>0.0001</td>
<td>1.09 (1.01, 1.18)</td>
<td>0.030</td>
</tr>
<tr>
<td>Smoking status</td>
<td>1.50 (0.93, 2.41)</td>
<td>0.095</td>
<td>2.39 (1.31, 4.38)</td>
<td>0.006</td>
</tr>
<tr>
<td>HAQ (0–3)</td>
<td>2.08 (1.57, 2.76)</td>
<td>&lt;0.0001</td>
<td>1.53 (1.06, 2.20)</td>
<td>0.022</td>
</tr>
<tr>
<td>Inclusion year</td>
<td>0.91 (0.84, 0.98)</td>
<td>0.015</td>
<td>0.84 (0.77, 0.92)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Age: age at inclusion in EAC cohort; gender: female vs male; erosive disease: >3 erosions scored on X-hand and feet (Sharp–van der Heijde score); smoking status: never smoked vs ever smoked (smoking in past and current).
was probably based on their relatively short follow-up time, making it an observation too early. This was confirmed by their second research, where they observed that excess mortality emerged after 10 years [27].

However, a recent study from the states suggested that excess mortality is caused by accelerated ageing and that this phenomenon is responsible for the fact that RA patients at onset of disease are already effectively > 2 years older than the general population [28], so if this is true one would have expected to observe excess mortality in the last period as well.

In conclusion, clinical practice in rheumatology has shown impressive progress with regard to treatment of signs and symptoms of RA as well as slowing down the rate of joint damage and prevention of functional disability. These current treatment strategies are characterized by rapid institution of appropriate treatment schedules, tight control of disease activity and combination therapies [7]. This study suggests an association between better care for patients with early RA and improved survival. As such it underlines the importance of early potent treatment strategies in comparison with wait-and-see policies.

Rheumatology key message

- Current treatment strategies seem to have a beneficial effect on the survival of early RA patients.

Acknowledgements

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