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Original article

Mortality over 14 years in MTX-refractory patients randomized to a strategy of addition of infliximab or sulfasalazine and hydroxychloroquine

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Abstract

Objective. To compare mortality risk over up to 14 years of follow-up in methotrexate-refractory patients with early RA randomized to a strategy starting with addition of infliximab *vs* addition of SSZ and HCQ.
Methods. Data was from the two-arm, parallel, randomized, active-controlled, open-label Swefot trial in which patients with early RA (symptom duration <1 y) were recruited from 15 rheumatology clinics in Sweden (2002–2005). Patients who did not achieve low disease activity after 3–4 months of MTX were randomized to addition of infliximab ($n = 128$) or SSZ and HCQ ($n = 130$). Participants were followed until death, emigration, or end of follow-up, whichever came first. Analyses were by intention-to-treat.
Results. Over an average follow-up of 13 years, there were 13 and 16 deaths, respectively [8.8 *vs* 10.6 deaths per 1000 person-years; mortality hazard ratio 1.2 (95% CI: 0.6, 2.5); $P = 0.62$]. The 1-year mortality was 0.8% in both treatment arms, the 5-year mortality was 2.3% for the infliximab arm compared with 1.5% for the conventional combination treatment arm, while the 10-year mortality was 7.8% and 7.7%, respectively. After 5 years, ∼50% of patients in the conventional combination therapy arm had switched to biologic treatment, and 50% in the biologic arm had discontinued treatment with a biologic DMARD.
Conclusion. No difference in mortality risk could be observed over up to 14 years of follow-up between treatment strategy groups. At 5 years (3 years after trial cessation), 50% of patients remained on their assigned therapy, reflecting that DMARD combination is an adequate treatment strategy in 50% of patients.
Trial registration. clinicaltrials.gov, identifier: NCT00764725.

Key words: mortality, rheumatoid arthritis, randomized controlled trial, register

Rheumatology key messages

- Data are limited on mortality risk in patients with early RA initiating a biologic treatment.
- Addition of biologic *vs* conventional DMARDs to methotrexate monotherapy does not affect mortality risk.

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Introduction

Among patients with RA, worse disease severity is associated with increased mortality [1]. Most studies continue to report that patients with established RA have a higher mortality rate than the general population [2–5], although some show trends of reduced excess mortality when compared with the general population [2].

Although long-term mortality for newly diagnosed RA patients has decreased over time, it remains elevated compared with the general population in both Canada

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[6] and Sweden [7]. A 23-year follow up of the COBRA trial demonstrated that intensive treatment of early RA using conventional therapies (MTX *vs* MTX+ SSZ) can provide long-term benefits [8]. Other studies have echoed the importance of early treatment, showing that, compared with late treatment, early treatment can reduce, but not eliminate, excess mortality over the long term [3].

Markers of disease activity and severity appear to be significant determinants of increased mortality in RA patients [9–11]. Although the management of RA has significantly improved since the introduction of biologic therapies [12], it remains unclear how this has affected patients' risk of death. While biologics improve disease activity control compared with MTX alone, not all patients are responsive to a first-choice biologic but end up switching to another biologic or a targeted synthetic DMARD. There are a number of trials comparing treatment strategies in early RA with regard to RA disease activity, but an almost total lack of studies that have gone on to report longer-term effects such as mortality.

Although some studies underline the potential mortality benefits of early treatment, there remains a scarcity of research that assesses the impact of modern treatment strategies. A 5-year follow up of incident RA patients showed that those diagnosed after the year 2000 appear to have reduced mortality risk compared with those diagnosed prior to 2000 [13]. Although the greatest increase in mortality risk appears to occur after 7–10 years of disease onset [9], it is possible that improved RA treatments along with a paradigm shift in RA management towards early, aggressive treatment, could have mortality benefits. Indeed, long-term mortality data from randomized strategy trials, irrespective of the strategy under study, are scarce to non-existent and it is particularly unclear how initial treatment strategy, in a treat-to-target setting, in early RA can affect risk of mortality. It is therefore unknown whether strategies starting with biologic treatment are associated with different mortality outcomes compared with strategies starting with non-biologic alternatives.

To better understand the impact of the early RA treatment strategy on long-term mortality, the aim of this study was to compare mortality risk over up to 14 years of follow-up between patients from the Swefot trial of early MTX-refractory RA, randomized to the addition of infliximab or the addition of SSZ and HCQ.

Methods

Participants

The Swefot trial has been described in detail elsewhere [14]. Briefly, adult patients (≥18 years of age) with early RA (symptom duration <1 year) were recruited from 15 rheumatology units across Sweden from 2002 to 2005. Key inclusion criteria were fulfilment of the 1987 American College of Rheumatology criteria [15], a disease activity score based on 28-joint count (DAS28) of >3.2 [16], no previous DMARD treatment, either absence or stably dosed oral glucocorticoid therapy for at least 4 weeks, and using at most 10 mg daily prednisolone (or equivalent). The main exclusion criterion was contraindications to any of the trial drugs. Patients were administered methotrexate and, after 3–4 months, those who had not achieved low disease activity were randomly allocated addition of either SSZ and HCQ or infliximab. Swefot was approved by the national health authorities/ethics committees at all sites and was conducted in accordance to the Declaration of Helsinki. All participants gave written consent prior to inclusion.

As previously reported, the addition of infliximab led to superior response according to EULAR criteria at 9 months [14] whereas no statistically significant difference was evident at 15 or 21 months after randomization [17]. Superior radiographical findings were demonstrated at 21 months in the infliximab group [17], while quality of life [18] and work loss [19] improved similarly for the two treatment strategies.

During the first 2-year trial period, included patients were scheduled for a visit at the rheumatology clinic at seven different time points. From years 3 through 7, data on treatment were collected from the Swedish Rheumatology Quality Register [20]. Randomized patients could discontinue the assigned treatment at any time for lack of effectiveness, side effects, or by own choice. Treatment was decided by the responsible rheumatologist in case of discontinuation and after the 2-year trial period.

As a benchmark, we also contrasted the Swefot patients with general population comparators identified from the Swedish Total Population Register [21]. Comparators were matched 5:1 to Swefot participants by age, sex, education and county of residence at index/diagnosis date.

Follow-up and outcome

For this study, we linked the Swefot trial database to the Swedish Total Population Register [21] and the Causes of Death Register with outcome data until 31 August 2017, resulting in mortality data for up to 14 years from inclusion. This register contains information on death date as well as the underlying and contributing causes of death for all persons registered as Swedish residents. Participants were followed until death, emigration (retrieved from the Total Population Register), or end of follow-up, whichever came first. Through these linkages, all deaths and emigrations during follow-up were detected.

Statistical analyses

Data were analysed by intention to treat, analysing all randomized patients according to their original treatment allocation, using Stata v14.0 (Stata Corp, TX, USA). We plotted Kaplan–Meier mortality curves to illustrate cumulative mortality, and used Cox regression to estimate hazard ratios with 95% CIs. The proportional hazards

Table 1 Characteristics of early RA patients randomized to addition of infliximab or conventional combination treatment

	Infliximab+MTX treatment (n = 128)	Conventional combination treatment (SSZ and HCQ) (n = 130)
Age (years), mean (S.D.)	51.9 (13.2)	53.7 (14.0)
Women, n (%)	97 (76)	101 (78)
Rheumatoid factor positive (%)	88 (69)	85 (65)
RA symptom duration at RA diagnosis (months), mean (S.D.)	10.1 (3.4)	10.1 (3.5)
DAS28[a], mean (S.D.)	4.9 (1.0)	4.8 (1.0)
HAQ[b], mean (S.D.)	0.9 (0.5)	1.0 (0.6)
EQ-5D utility (18)[c]		
Mean (S.D.)	0.51 (0.29)	0.55 (0.27)
Median (25th–75th)	0.62 (0.29–0.73)	0.62 (0.52–0.73)
Minimum–maximum	−0.18 to 1.00	−0.24 to 1.00
Education, n (%)		
<10 years	19 (15)	26 (20)
10–12 years	71 (55)	63 (48)
>12 years	30 (23)	30 (23)
missing	8 (6)	11 (8)
Smoking[d], n (%)	33 (26)	30 (23)
Comorbidity[e], n(%)		
Infection	16 (12.5)	7 (5.4)
Malignancy	0 (0)	2 (1.5)
Cardiovascular disease	2 (1.6)	5 (3.8)
Diabetes[f]	4 (3.1)	4 (3.1)
Depression/anxiety disorer	4 (3.1)	2 (1.5)
Hypertension[g]	8 (6.3)	11 (8.5)
Hip or knee prosthesis	2 (1.6)	3 (2.3)

[a]28-joint count disease-activity score. [b]HAQ; missing HAQ data for four patients in the infliximab arm and two patients in the conventional combination treatment arm. [c]EuroQol 5-Dimensions, UK preference set. Missing EQ-5D information for 21 patients in the infliximab treatment group and for 13 patients in the conventional combination treatment group. [d]Missing smoking information for five patients in the infliximab arm and for four patients in the conventional combination treatment arm. [e]Comorbidities up to 5 years before start of follow-up. Comorbidity based on outpatient (includes 1 year prior to follow-up) or inpatient visit (includes 5 years prior to follow-up) with corresponding ICD10 Codes (retrieved from: National Patient Register). [f]A diagnosis of diabetes was assumed if ATC (Anatomical Therapeutic Chemical) classification system prescription code of insulin or oral diabetes drugs (retrieved from: Swedish Prescribed Drug Register). [g]Hypertension diagnosis assumed if ATC classiciation system prescription code of antihypertensive drug (retrieved from: Swedish Prescribed Drug Register).

assumption was tested by introducing an interaction term for treatment group and follow-up time.

Results

Participant characteristics

Between October 2002 and December 2005, a total of 493 patents with new-onset RA were screened for inclusion. After screening, 487 patients entered the run-in period receiving methotrexate monotherapy. Of the 258 patients with DAS28 > 3.2 at the end of the 3–4 month run-in period, which was the definition of insufficient response to MTX, 128 were randomized to the addition of infliximab, and 130 to the addition of conventional combination therapy (SSZ and HCQ). At randomization, there were no significant between-group differences in patient characteristics or comorbidities (Table 1).

In our study, after 5 years, ~50% of patients allocated to conventional combination treatment had initiated biologics and 50% allocated to infliximab had discontinued use of a biologic (Fig. 1).

Follow-up and outcome

During a median follow-up of 12.8 years in the infliximab arm and 12.9 years in the conventional treatment arm, there were 13 and 16 deaths, respectively (Table 2). The mortality rates were 8.8 (95% CI: 0.0, 25.1) per 1000 person-years in the infliximab arm, and 10.6 (95% CI: 0.0, 28.4) in the conventional combination treatment arm, respectively; mortality hazard ratio 1.2; 95% CI: 0.6, 2.5; P =0.62 (Table 2 and Fig. 2). The test of whether the proportional hazards assumption was violated was not statistically significant (P =0.43), but the mortality curves for the two treatments crossed after about 11 years of follow-up.

The 1-year mortality was 0.8% in both treatment arms, the 5-year mortality was 2.3% for the infliximab arm compared with 1.5% for the conventional

Fig. 1 Drug survival in Swefot patients over up to 8 years' follow-up

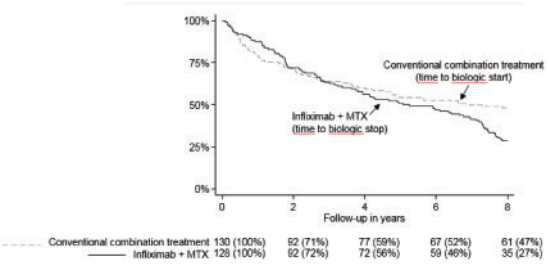

Fig. 2 Cumulative incidence of death over up to 14 years of follow-up in the Swedish Swefot trial

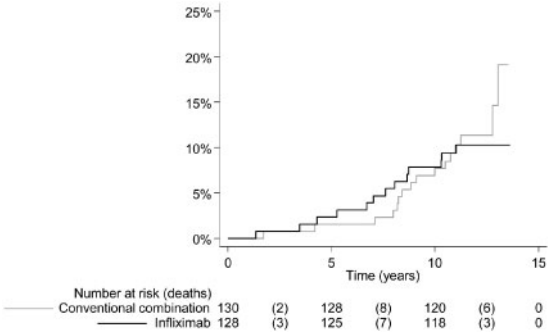

Table 2 All-cause mortality over up to 14 year follow-up, by initial treatment arm allocation

	Infliximab+MTX treatment ($n = 128$)	Conventional combination treatment[a] ($n = 130$)
n	128	130
n deaths	13	16
n loss to follow-up	0	0
Sum follow-up (years)	1477	1504
Deaths per 1000 person years	8.8	10.6
	(95% CI: 0.0, 25.1)	(95% CI: 0.0, 28.4)
Causes of death (*n*)		
Infection	0	2
Malignancy	7	3
Cardiovascular disease	1	4
Pulmonary disease	2	2
Hematological	1	0
Neurodegenerative	0	1
Other	1	0
Missing[b]	1	4

[a]Co, nventional combination treatment: methotrexate with the addition SSZ and HCQ. [b]Information on deaths that occurred in 2016 was not available.

combination treatment arm, while the 10-year mortality was 7.8% and 7.7%, respectively.

When comparing Swefot patients with age, sex, education and location-matched general population comparators, RA patients had no statistically significant increased or decreased risk of death (mortality hazard ratio 0.8; 95% CI: 0.6, 1.0; $P = 0.09$).

Discussion

In this study, we took advantage of the possibility to accomplish complete (zero loss to follow-up) long-term mortality follow-up via registers among patients enrolled in an early RA strategy trial in a country with universal access to health care. After two years, treatment was decided by the responsible rheumatologist. This study compared initial treatment strategy rather than specific drug regimens over 12 years' follow-up in real life after trial cessation. The results indicated little difference in all-cause mortality over the decade following randomization [7]. To our knowledge, this is one of the first studies of its kind in which long-term mortality in patients with early RA has been deterministically assessed during extended follow-up of a randomized strategy trial.

Swefot is a good population to address this question, because the treatment strategy that was applied in the two-year trial is in accordance with today's treatment guidelines in early RA, and the patients have thereafter been followed in registers in Sweden, where there is equal access to health-care and treatment decisions made on clinical grounds.

No or minor differences in treatment effect and adverse events

It has long been hypothesized that a treatment strategy immediately starting with infliximab after insufficient MTX response would result in better health outcomes by better control of disease activity and slower radiological progression than conventional DMARD treatment. Because no difference in disease activity between infliximab and conventional combination treatment could be detected beyond the first year in the Swefot study [18] and in other studies of TNF inhibitors compared with combination DMARD treatment [22–24], the absence of a survival benefit may not be surprising, although better 2-year radiological outcomes were observed with infliximab in Swefot [14]. Importantly, no increased mortality risk from the strategy starting with infliximab could be detected either, which is in line with the similar adverse event profiles of the different treatments [14].

Crossover

We used the intention-to-treat principle, analysing all randomized patients according to their random allocation to make a strategy comparison of early RA patients starting with addition of infliximab *vs* starting with addition of conventional DMARDs after MTX failure, but

allowing and expecting multiple treatment changes over the long follow-up. As adherence to originally assigned treatment is likely to be associated with the underlying risk of death (e.g. via insufficient RA disease control), we did not consider using as-treated, per-protocol, or on-treatment approaches [25].

Over time, the more similar the treatment strategy arms became due to crossovers, diluting the possibility of detecting potential strategy-specific differences. Unless the initial treatment strategy is associated with long-term consequences of any differential effectiveness, cross-over would make the treatment arms indistinguishable. Such effects are, however, both plausible ('window of opportunity') and important to assess.

The large number of crossovers in our study are likely the result of physicians practicing today's treatment guidelines which, at least partly, follow a treat-to-target paradigm. Those who remained longer on their allocated treatment throughout follow-up are likely to have different disease characteristics than those switching. Effectiveness-related mortality improvements from early disease control in the non-switching group are likely to be offset by the relative lack of disease control among switchers. Our results do not, however, provide any evidence that the net effects on mortality would differ by treatment strategy.

Conclusion

No difference in mortality risk could be observed over up to 14 years of follow-up in patients with MTX-refractory early RA randomized to a strategy starting with addition of infliximab compared with a strategy starting with conventional combination treatment.

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