Is there an anti-inflammatory effect of statins in rheumatoid arthritis?

Analysis of a large routinely collected claims database

Sara Lodi,¹ Stephen J. W. Evans,¹ Peter Egger² & James Carpenter¹

¹London School of Hygiene and Tropical Medicine, London and ²GlaxoSmithKline Epidemiology, Greenford, UK

Correspondence

Dr Sara Lodi, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK.
Tel: +44 20 7670 4772
Fax: +44 20 7670 4685
E-mail: sal@ctu.mrc.ac.uk

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The increasing evidence of the anti-inflammatory action of statins has stimulated interest in whether these might be beneficial in disease management of rheumatoid arthritis (RA), a chronic diseases characterized by high levels of inflammation.
- The TARA trial (McCarey 2004) suggested a significant reduction in disease activity outcomes in RA patients randomized to atorvastatin compared with those assigned to the placebo harm.
- However, as the signal reported by the trial was small, more evidence is needed.

WHAT THIS PAPER ADDS

- We investigated the possible anti-inflammatory effect of statins in a cohort of RA patients using a large health insurance claims database.
- To our knowledge, this is the largest study ever conducted on the anti-inflammatory effects of statins.
- Our data do not show any beneficial effect of statins in reducing disease inflammation in RA patients.

AIM

To investigate the possible anti-inflammatory effect of statins in a cohort of rheumatoid arthritis (RA) patients.

METHODS

We conducted a cohort study consisting of all patients with at least one claim for RA using LifeLink, a health insurance claims database. Initiation and cessation of oral steroid (OS) therapy were treated as surrogate for inflammatory flare-up and controlled inflammation, respectively. We split the RA patients into two sub-cohorts based on whether they were using OS within a specified time window of the RA index date (first recorded claim for RA in the database). Cox proportional hazard models were used to evaluate the association between time-varying exposure to any statins and (i) initiation of OS therapy in the non-users of OS at RA index date and (ii) cessation of OS therapy in the users of OS at RA index date controlling for potential confounders.

RESULTS

We found 31 451 non-users of OS at RA index date and 6026 users of OS within the time window at RA index date. The results on both sub-cohorts were both consistent with no association of statin exposure with the risk of initiation/cessation of OS: the hazard ratio (HR) of initiating OS therapy was 0.96 (95% confidence interval 0.9, 1.01) in the sub-cohort of non-users and the HR of cessation of OS therapy was 0.95 (0.87, 1.05) in the sub-cohort of users of OS therapy at RA diagnosis.

CONCLUSIONS

These data do not show any beneficial effect of statins in reducing disease inflammation in RA patients.

Introduction

Statins, introduced to the market as lipid-lowering agents, have been shown to reduce cardiovascular morbidity and mortality [1–7]. However, there is growing evidence that the beneficial effect of statins cannot be merely explained by their beneficial effect on lipids [3, 4, 7, 8]. One of the other plausible mechanisms is anti-inflammatory [9–13].

This possible anti-inflammatory action has stimulated interest in whether statins might be beneficial in routine disease management of rheumatoid arthritis (RA) [14–16]. As statins have a good safety profile, if beneficial they could routinely be given to RA patients to help control disease inflammation. This has the potential to reduce the need for the relatively toxic long-term treatments currently used for RA, such as several disease-modifying antirheumatic drugs (DMARDs).

The aim of this study was to investigate any possible anti-inflammatory effect of statins in RA patients. The data source is a large US health insurance claims database called LifeLink. Since this database does not contain data on current inflammation status, we used the prescription of oral steroids (OS) as a surrogate for such status.

Methods

Data source

Lifeline is a US medical and pharmacy claims database recording the insurance claims of 1.8 million employees, their dependents and retirees within an employer health-care insurance scheme. The database reports basic information on eligibility for care, demographic characteristics, and both in- and outpatient medical and pharmacy claims. At any one time, patients are enrolled on one of two levels of insurance coverage (partial or full) and one of the two health plan types [indemnity or preferred provider organizations (PPO)]. Indemnity health plan is based on the fee-for-service payment at a designed rate, whereas PPO is based on negotiated fixed rates. The version of the database used consists of all paid medical and pharmacy claims from 1 January 1991 to 31 December 2002. Within the database we identified a study population of patients with at least one medical claim for RA. In order to exclude cases with juvenile RA, eligible patients had to be aged > 20 years. Furthermore, as in our data information on pharmacy claims collected before 1993 was less accurate due to a change in the recording procedure, eligible patients had to present a claim for RA after December 1992.

Study design

We defined as RA index date the date of the first medical claim for RA, a proxy of RA diagnosis. As information on

inflammatory status is not available in LifeLink, we treated the prescription of OS (prednisone and its derivatives) as a surrogate for inflammation status. Start of OS use is thought to mark the start of the inflammatory bout well, since OS is commonly prescribed to keep inflammation under control. Furthermore, because of the side-effects of long-term use of OS, such treatment is discontinued as soon as the inflammation is under control. Hence, if statins have anti-inflammatory properties, they should reduce the chance of initiation of OS therapy and should increase the chance of cessation of OS therapy in those RA patients currently on OS.

We split the eligible patients into two mutually exclusive sub-cohorts based on whether they were not or were using OS in a time window of RA index date ± 30 days (details in Appendix 1). The rationale for this time window was that recorded dates of prescription and diagnosis may not be exact. Sub-cohort I included patients not on OS therapy during the designated time window. The outcome event was the initiation of OS therapy defined as the first pharmacy claim for an OS. Sub-cohort II included patients who were on OS therapy during the designated time window around RA index date. The outcome event for this cohort was the cessation of OS therapy. This was defined as the date of the end of the first OS prescription that was not followed by a subsequent prescription within 45 days. The end of an OS prescription was defined as the date of the prescription plus its duration as indicated in the claim (Appendix 2).

The rationale for the separate analysis of initiation and cessation of OS therapy is that potential confounding may work differently in the two scenarios. For example, some predictors for initiation of OS therapy might not be the same as those for cessation of OS therapy. Therefore, if the sub-cohorts give compatible conclusions about the association between statin therapy and OS use, we can be more confident about a causal link.

Exposure

We defined current exposure as a minimum exposure to 30 days of uninterrupted statin therapy (Figure 1). To account for the fact that patients who start statin therapy might stop and restart it later, we defined statin exposure as a time varying covariate. Exposure to any statin is regarded as a step function taking value 1 when the subject is under statin therapy and 0 otherwise. Patients who had only one statin prescription were considered as unexposed throughout their follow-up as it is possible they did not take all the doses from the first prescription. Two prescriptions were considered continuous if there were <30 days between the end of a first prescription and the initiation of the second. An exposure period ended when the gap between the end of one prescription and the next was >30 days. Thus the end of the statin exposure period was: time of the end of the last prescription +30 days.

Figure 1

Pictorial representation of assessment of statin exposure in (a) sub-cohort I [non-users of oral steroids (OS) at rheumatoid arthritis (RA) index date] and (b) sub-cohort II (users of OS at RA index date). Current statin exposure is defined as a minimum exposure to 30 days of uninterrupted statin therapy

Statistical analyses

Cox proportional hazards models were used to evaluate the association between time-varying exposure to statins and (i) initiation of OS therapy in the non-users of OS at RA index date (sub-cohort I) and (ii) cessation of OS therapy in the users of OS at RA index date (sub-cohort II). As changes in medical coverage or health plan may have an impact on the risk of receiving a prescription, follow-up was censored at the earliest of: the date of change in medical coverage and/or health plan, the date of end of eligibility for care, and 31 December 2002. To account for the progressive nature of the disease, the time origin was defined as RA index date in both cohorts. Given the left truncation of the data, it is not possible to know definitively whether patients were prevalent or incident RA cases at RA index date. We used a graphical approach to classify patients as incident or prevalent RA cases at RA index [17], based on the plot of the incidence rates over time from database enrolment. The method suggests classifying as 'prevalent' RA cases those patients whose RA index date falls within 6 months of the start of their eligibility period and 'incident' RA cases those RA patients whose RA index date falls at least 6 months after the start of their eligibility period.

The regression models were adjusted by gender, indicator for RA incident cases (as defined above), medical coverage (full vs. partial) and health plan (indemnity vs. PPO scheme), and, to account for the secular trend in use of statins and changes in RA management over the period of the study, calendar year of RA index date (1992–2002). Moreover, the models were adjusted by co-medications in the year before RA index date [nonsteroidal anti-inflammatory drugs (NSAIDs), DMARDs, angiotensin converting enzyme inhibitors, statin, thiazide, loop diuretics, warfarin, β -blockers, oral antidiabetics and insulin] and comorbidities ever recorded before RA index date [diabetes mellitus, autoimmune disease other than RA, osteoarthritis, asthma, chronic obstructive pulmonary disease (COPD), peptic ulcer, myocardial infarction, cerebral haemorrhage, angina, transient ischaemic attack, stroke, hyperlipidaemia, hypertension, pulmonary circulation disease, liver disease, heart failure] and oral steroids ever prescribed before RA index date. More parsimonious models were selected by retaining covariates with P -value < 0.1 in the full model adjusted for all the covariates. The models were stratified by age at RA index date (20–50, 51–70 and 71–88) as this was found necessary for proportional hazards [18].

Sensitivity analyses

Patients who discontinued statins may be a selected group whose hazard of OS initiation/cessation could differ from those who have never been dispensed a statin. Moreover, statin use may irreversibly change the inflammatory status. Therefore, we refitted the models with the following definition of exposure: at each event time we defined a patient as currently exposed to statins if on statin therapy at that time. If instead a patient was not currently on statins then they were classified either as a past statin user if they had a record of previous statin use or else as never exposed.

We defined current exposure as a minimum exposure to 30 days of statin therapy. However, we cannot exclude the possibility that statin exposure might need a longer time than 30 days to exhibit an anti-inflammatory effect in RA. Therefore, we re-analysed both sub-cohorts by changing the definition of minimum (uninterrupted) duration of exposure from 30–45 and 100 days.

Our definition of RA 'diagnosis' required at least one record (i.e. claim) for RA. Thus we might have included patients with a single claim 'for RA' who actually did not have RA. To investigate this, we repeated the analyses including only those patients who had at least one further diagnostic record for RA at least 1 week after RA index date and within a time window defined as follows. For non-users of OS at RA index date 400 days is an appropriate window to retain patients who had an appointment scheduled 1 year after their initial visit. For users of OS at RA index date 100 days seems a reasonable time window given that these patients are on OS therapy at RA index date and that they have to consult a doctor for a repeat OS prescription.

Finally, as diseases like autoimmune disease, asthma and COPD are often treated with OS, we re-estimated the effect of statins in the subgroup of individuals who did not present a record for these comorbidities at RA index date.

Results

After splitting patients according to their use of OS at RA index date, we found 31 451 non-users of OS at RA index date and 6026 users of OS at RA index date. Amongst the 31 451 non-users of OS at RA index date, during a follow-up of 99 748.77 person-years 11 402 (36%) began OS therapy during their follow-up, and median (interquartile range) time to initiation of OS was 6.8 years (2.08, –). Amongst the users of OS at RA index date, 5490 (91%) ceased OS therapy during their follow-up of 4410.3 person-years. The median time to OS cessation 0.37 years (0.19–0.89).

Patients' characteristics for the two sub-cohorts are presented in Table 1. The two sub-cohorts differed in several baseline characteristics. The users of OS at RA index date had higher rates of pharmacy and medical claims,

they were treated more frequently with RA medications before RA index date, and were slightly more likely to be defined as prevalent RA patients.

Table 2 shows the final model fitted in the sub-cohort of non-users of OS at RA index date. Here, a hazard ratio (HR) < 1 indicates a protective effect of the covariate on initiating OS therapy consistent with a possible anti-inflammatory effect. In this sub-cohort, the adjusted HR for statins of initiating OS therapy was 0.956 [95% confidence interval (CI) 0.901, 1.015], hence statin use only slightly and statistically nonsignificantly reduced the likelihood of start of OS therapy. Baseline records for diseases treated with OS like autoimmune disease, asthma and COPD were associated with an increased likelihood of initiating OS therapy. On the other hand, cardiovascular diseases such as cerebral haemorrhage and stroke, diabetes and hypertension were associated with a decreased likelihood of initiating OS therapy.

Table 3 presents the final model for users of OS at RA index date. Here, as the outcome was cessation of OS therapy, a protective effect of a covariate is indicated by a HR > 1 consistent with an anti-inflammatory effect. The adjusted exposure HR of cessation of OS therapy for statin use was 0.954 (95% CI 0.866, 1.051), indicating that statin use had only a small and statistically nonsignificant 'prolonging' effect on OS use. Cardiovascular diseases such as angina, hypertension and, to a lesser extent, myocardial infarction were significant predictors of cessation of OS therapy.

Both final estimates were very similar to the unadjusted HRs, which were 0.980 (95% CI 0.925, 1.038) and 0.955 (95% CI 0.872, 1.051) for non-users and users of OS at RA index date, respectively.

We then explored the effect of statin exposure on OS therapy further by distinguishing between current and past exposure. For the non-users of OS at RA index date, the HR for current exposure was almost unchanged (HR 0.97, 95% CI 0.911, 1.032) when the reference category was never exposed to a statin. No difference in hazard was found between past and never exposed to statins (HR 1, 95% CI 0.929, 1.076). For the users of OS at RA index date, the effect of current exposure did not change when the reference category was never exposed to statins (HR 0.96, 95% CI 0.87, 1.06). However, patients with a record of past exposure presented a slightly larger hazard of OS cessation compared with patients never exposed to statins (HR 1.10, 95% CI 0.99, 1.21).

Changing the minimum exposure from 30 to 45 days and 100 days for non-users of OS at RA index date led to HR of initiation of OS therapy of 0.972 (95% CI 0.912, 1.036) and 0.96 (95% CI 0.895, 1.029) and for the users of OS at RA index date led to HR of cessation of OS therapy of 0.91 (0.820, 1.020) and 0.836 (0.728, 0.967), respectively.

When we re-analysed excluding individuals with any record of asthma, COPD and autoimmune disease at RA

Table 1

Patient characteristics

	Non-users of OS at RA index date (n = 31 451) n (%)	Users of OS at RA index date (n = 6026) n (%)
Database related and demographic information		
Female	20 627 (66)	3947 (66)
Full medical coverage	13 895 (44)	2685 (45)
Indemnity health plan	23 571 (75)	4626 (77)
Incident RA cases	26 416 (84)	4665 (77)
Number of medical claims in the year before RA		
0	1 716 (5)	226 (4)
1–10	9 781 (31)	1497 (25)
11–20	7 462 (24)	1401 (23)
21–30	4 514 (14)	1011 (17)
31–40	2 671 (8)	601 (10)
41+	5 307 (17)	1290 (21)
Number of pharmacy claims in the year before RA		
0	1 827 (6)	71 (1)
1–10	6 734 (21)	740 (12)
11–20	6 102 (19)	1047 (17)
21–30	5 112 (16)	966 (16)
31–40	3 612 (11)	877 (15)
41+	8 064 (26)	2325 (39)
RA index date		
1993	6 827 (22)	1163 (19)
1994	3 807 (12)	661 (11)
1995	3 251 (10)	584 (10)
1996	2 816 (9)	520 (9)
1997	2 739 (9)	559 (9)
1998	2 866 (9)	509 (9)
1999	2 655 (8)	563 (9)
2000	2 449 (8)	527 (9)
2001	2 178 (7)	536 (9)
2002	1 863 (6)	404 (7)
Age at RA index date median [IQR]	60 [51, 71]	62 [53, 72]
Medication one year before RA ID		
Statins	972 (3)	180 (3)
NSAID	2 772 (9)	780 (13)
DMARD	1 433 (5)	946 (16)
Fibrate	110 (0)	23 (0)
Digoxin	346 (1)	93 (2)
Heparin	17 (1)	2 (0)
Loop diuretic	431 (1)	115 (2)
Thiazide	550 (2)	122 (2)
ACE inhibitors	1 061 (3)	271 (5)
Potassium sparing	62 (0)	7 (0)
Warfarin	437 (1)	73 (1)
Clopidogrel bisulphate	165 (1)	63 (1)
β-Blockers	476 (2)	41 (1)
Angiotensin	275 (1)	71 (1)
Insulin	174 (1)	54 (1)
Antidiabetic	406 (1)	93 (2)
OS (ever before RA ID)	8 731 (28)	4261 (71)
Diagnostic code before RA ID		
Diabetes	8 517 (27)	1359 (23)
Autoimmune disease	5 863 (19)	1621 (27)
Osteoarthritis	13 434 (43)	2836 (47)
Asthma or COPD	10 928 (35)	2330 (39)
Peptic ulcer	2 558 (8)	509 (8)
Myocardial infarction	2 083 (7)	450 (7)
Cerebral haemorrhage	691 (2)	110 (2)
Angina	7 344 (24)	1388 (23)
Transient ischaemic attack	2 043 (7)	394 (7)
Stroke	4 256 (14)	803 (13)
Hyperlipidaemia	13 067 (42)	2251 (37)
Pulmonary circulation disease	1 225 (4)	307 (5)
Hypertension	16 163 (42)	2947 (49)
Heart failure	4 142 (13)	869 (14)
Liver disease	3 759 (12)	687 (11)

OS, oral steroids; RA, rheumatoid arthritis; NSAID, nonsteroidal anti-inflammatory drug; DMARD, disease-modifying antirheumatic drug; COPD, chronic obstructive pulmonary disease.

Table 2

Sub-cohort I. Non-users of OS at RA index date

	Hazard ratio	95% CI	P
Current statin exposure	0.956	0.901 1.015	0.140
Diabetes	0.8	0.764 0.839	<0.001
Autoimmune disease	1.086	1.035 1.139	0.001
Asthma or COPD	1.23	1.18 1.281	<0.001
Cerebral haemorrhage	0.771	0.664 0.896	0.001
Stroke	0.915	0.859 0.975	0.006
Hypertension	0.873	0.838 0.91	<0.001
Heart failure	0.932	0.874 0.994	0.032
DMARD	1.438	1.348 1.549	<0.001
Angiotensin	1.262	1.171 1.568	0.035
Change in medical coverage	1.089	1.009 1.176	0.030
Incident at RA index date	0.76	0.723 0.799	<0.001
Female	1.072	1.019 1.116	0.001
Number of medical claims 1 year before RA ID			
0	0.856	0.769 0.954	0.005
1–10	0.59	0.807 0.915	<0.001
11–20	0.929	0.873 0.988	0.018
21–30	0.953	0.892 1.018	0.150
31–40	0.947	0.878 1.022	0.170
≥41	1		
Number of pharmacy claims 1 year before RA ID			
0	0.476	0.426 0.533	<0.001
1–10	0.635	0.596 0.676	<0.001
11–20	0.737	0.696 0.781	<0.001
21–30	0.834	0.787 0.884	<0.001
31–40	0.894	0.84 0.952	<0.001
≥41	1		
Year of RA index date			
1993	1		
1994	0.948	0.891 1.009	0.093
1995	0.903	0.844 0.968	0.004
1996	0.891	0.828 0.959	0.002
1997	0.936	0.867 1.009	0.086
1998	0.893	0.825 0.967	0.005
1999	0.906	0.833 0.986	0.022
2000	0.848	0.772 0.932	0.001
2001	0.844	0.756 0.942	0.003
2002	0.728	0.608 0.872	0.001

Outcome event is cessation of OS therapy. Cox model stratified by age, whether patients had a OS before RA index date, and whether they took a NSAID before RA. HR < 1 indicates a protective effect of statins. DMARD, disease-modifying antirheumatic drug; COPD, chronic obstructive pulmonary disease; OS, oral steroids; RA, rheumatoid arthritis.

index date, the estimated HRs were 0.946 (95% CI 0.874, 1.041) and 0.986 (95% CI 0.857, 1.074) for non-users and users of OS at RA index date, respectively, very similar to those found without this exclusion criterion.

For non-users of OS at RA index date, restricting the analysis to patients who had at least two diagnostic records for RA within 400 days for the non-users of OS at RA index date and 100 days for users of OS at RA index date led to no major changes in the estimates. For non-users the HR of initiating OS therapy was 0.983 (95% CI 0.886, 1.091), while for current users the HR of cessation of OS therapy was 0.927 (95% CI 0.778, 1.105).

Table 3

Sub-cohort II. Users of OS at RA index date

	Hazard ratio	95% CI	P
Current statin exposure	0.954	0.866 1.051	0.340
Peptic ulcer	1.168	1.059 1.289	0.002
Myocardial infarction	1.12	1.005 1.247	0.041
Hypertension	1.096	1.033 1.163	0.003
Liver disease	1.152	1.057 1.256	0.001
OS (before RA ID)	0.748	0.7 0.799	0.000
DMARD	0.91	0.844 0.981	0.014
Thiazide	1.147	0.949 1.386	0.160
Incident RA case	1.455	1.344 1.576	<0.001
Female	1.12	1.058 1.186	<0.001
Number of medical claims 1 year before RA ID			
0	1.592	1.234 2.054	<0.001
1–10	1.466	1.327 1.619	<0.001
11–20	1.218	1.122 1.323	<0.001
21–30	1.105	1.018 1.199	0.017
31–40	1.098	1.01 1.192	0.027
≥41	1		
Year of RA index date			
1993	1		
1994	0.958	0.862 1.065	0.420
1995	0.853	0.761 0.955	0.006
1996	0.859	0.763 0.967	0.012
1997	0.881	0.783 0.99	0.034
1998	0.992	0.816 1.041	0.190
1999	0.947	0.842 1.066	0.370
2000	0.948	0.84 1.069	0.380
2001	0.998	0.883 1.128	0.980
2002	1.311	1.137 1.512	<0.001

Outcome event is cessation of OS therapy. Cox model stratified by age and whether patient had angina before RA index date. HR > 1 indicates a protective effect of statins. DMARD, disease-modifying antirheumatic drug; OS, oral steroids; RA, rheumatoid arthritis.

Discussion

Several studies have suggested that statins have anti-inflammatory properties. Early evidence comes from laboratory experiments *in vitro* and from animals [19–21]. Furthermore, statins have been shown to reduce the level of C-reactive protein (CRP) in humans independently of the achieved reduction of low-density lipoprotein-cholesterol levels [9, 10]. Recently, the anti-inflammatory effects of statins have been investigated in humans with diseases characterized by high levels of inflammation such as organ transplantation [22–24], multiple sclerosis [25], sepsis [26] and RA [14, 27], indicating beneficial effects. On the other hand, no significant benefit has been found in patients with giant cell arthritis [28]. Despite this body of evidence, it is not clear whether statins should be employed in the routine management of RA patients in order to control disease inflammation and to reduce the need of other treatments that can have serious side-effects when taken long-term.

In this study we explored possible secondary anti-inflammatory effects of statins in RA patients using a large

routinely collected US claims database. Our findings provide no evidence of association between statin exposure and OS use. Assuming that OS is a reasonable marker for change in inflammation status and that we are able to control for the principal confounders, our study has shown no evidence of an anti-inflammatory effect of statins in RA patients. As initiation and cessation of OS therapy are markers for an increase and decrease in the underlying RA inflammatory process, we evaluated the effect of statin exposure on both initiation and cessation of OS therapy. In order to do this, we split the eligible patients into two sub-cohorts: the non-users of OS at RA index date were followed until initiation of OS therapy, while the users of OS at RA index date were followed until cessation of OS therapy. Neither analysis provided evidence of an effect of statins on OS use. To investigate whether the lack of evidence was due to an incorrect definition of statin exposure or to inappropriate inclusion criteria, we conducted several sensitivity analyses. These analyses all supported the original conclusion.

A key strength of this study is its large sample size. As far as we know, this is the largest study of the anti-inflammatory effects of statins in RA patients. Thus, the lack of evidence in favour of an anti-inflammatory effect of statins is not due to lack of statistical power. Our power calculations showed that in the group of non-users at RA index date the sample size was large enough to detect as significant, with 80% power, a HR of ≤ 0.92 .

An inevitable limitation is the observational design, which may have unmeasured confounding. However, as the sub-cohorts differed substantially in terms of predictors of OS use, we expect that some confounding mechanisms might work differently in the two sub-cohorts. Even though the direction of the point estimates in the sub-cohorts is different – suggesting among patients exposed to statins a reduction of OS use in the cohort of non-users of OS at RA index date and an increased use of OS in the cohort of users of OS at RA index date – the results are overall concordant with a nonsignificant anti-inflammatory effect of statins. As the results point to a similar conclusion, we believe that unmeasured confounding is unlikely to have played a major role in the outcome.

Further limitations mostly relate to the nature of the healthcare database used. First, there are no validation studies regarding the accuracy and completeness of the data. This could, for example, result in under-ascertainment of exposure, measurement error in time at risk for an outcome event and misclassification of patient characteristics in terms of medication or morbidity history. In turn, this could cause imprecise final effect estimates. Second, there was no information on the use of over-the-counter NSAIDs and aspirin, smoking, obesity and disease severity. Nevertheless, using a simulation study we looked at the effect of measurement error of various magnitudes on statistical power and concluded that it was unlikely that we missed a clinically meaningful effect of statins on change

in inflammation because of the noise. Finally, we found that in some Cox models the proportional hazards assumption was violated. We re-analysed the data using the accelerated failure time model, which does not have the same assumptions. Our conclusions remained unchanged.

Under the assumption of causal effect of statins in reducing inflammation, we would expect (i) lower HR of beginning OS therapy and (ii) higher HR of cessation of OS therapy with increasing duration of statin use. The relation between duration of exposure and risk of the outcome was addressed in a sensitivity analysis where we re-analysed both sub-cohorts by changing the definition of minimum (uninterrupted) duration of statin use from 30 to 45 and 100 days. The results from these sensitivity analyses did not change our conclusions regarding the effect of statins. As we did not find any trend due to the definition of exposure, we concluded that further analyses aimed at exploring duration (e.g. proportion of time under statin therapy out of the last 360 days) were not necessary.

Our conclusions contrast with two recent studies: the TARA trial [14] and the case-control study by Jick *et al.* [27].

TARA [14] was a randomized controlled trial (RCT) that studied the effect of statins in RA patients. It reported that patients randomized to statins had a small but significant decrease in the primary outcome [Disease Activity Score (DAS) 28 score] and a significant decrease in CRP and number of swollen joints compared with placebo. However, when looking at the results on clinical markers such as tender joint count, early morning stiffness, visual analogue score, patient global assessment, health assessment questionnaire, patients randomized to statins did not differ significantly from controls.

The discrepancy between the findings from the RCT and our study could be due to different definitions of the outcome change in inflammation. In our study, change in inflammation was measured as initiation or cessation of OS therapy. In the TARA study change in inflammation was measured as change in DAS28 score, a composite measure of inflammation status. This issue could have been solved only if we were able to compare the change in OS intake in patients in the two arms of TARA study or if we were able to measure DAS28 score in a subset of RA patients in the LifeLink data.

Jick *et al.* [27] explored the potential protective effect of statins on the incidence of RA in patients with hyperlipidaemia. The adjusted odds ratio for development of RA in subjects taking statins compared with those not taking statins was 0.59 (0.37–0.96). Various aspects could have led to the discrepancy between our findings and those of Jick *et al.*

First, despite the effort of Jick *et al.* to control for confounding at the design and analysis stage, there could be residual confounding due to the healthy user bias. This has been suggested as a potential source of bias in observational studies of the association between use of statins and reduced risk of hip fractures [29], sepsis [26] and cancer

[30]. According to this hypothesis, patients who are in better health and therefore at lower risk of developing RA are more likely to request, be prescribed and persist with statin therapy. In our study, the direction of our finding does not support this kind of bias. In fact, the effect of healthy behaviour in our study would be an overestimate of the beneficial effects of statins in RA inflammation: patients with healthy behaviours (e.g. nonsmokers) would be more likely to be given and adhere to statins, but also less likely to have severe disease progression and thus less likely to initiate OS therapy/more likely to stop OS therapy.

Second, as Jick *et al.* estimated the effect of statin exposure on the incidence of RA rather than disease progression, the two studies were based on very different study groups. If statins reduced the risk of RA onset, then patients in our study would be a particular selection of patients: (i) with previous use of statins but less susceptible to their anti-inflammatory effects and (ii) without previous use of statin. While it is not possible to check the first point, this would probably only be a problem if statin use substantially delayed or postponed the onset of RA. There is no evidence of this; reported possible benefits of statins are relatively small. Regarding (ii), our findings were confirmed when, as a sensitivity analysis, we repeated the analyses on the subgroup of individuals without any previous use of statin at RA index date.

Putting together the results from the TARA trial and our study, we conclude that if statins have a beneficial effect in controlling disease inflammation and decreasing disease manifestations in RA patients, this must be much smaller than the effect of DMARDs and other drugs used to manage the disease.

In summary, these data do not provide evidence in support of a beneficial effect of statins in controlling disease progression in patients with RA.

Competing interests

None to declare.

P.E. is an employee of and has shares in GlaxoSmithKline. J.C. has provided consultancy and training to GlaxoSmithKline, Pfizer and Boehringer Ingelheim, Novartis and Bayer Pharmaceutical companies, and has received PhD student-ship funding from GlaxoSmithKline and Amgen. We thank GSK for providing data and support of the PhD of S.L. We also thank Frank DeVries for his helpful comments.

Appendix 1

In this section we describe how we extracted two mutually exclusive sub-cohorts of users and non-users of OS at RA index date. Our aim was to divide the eligible RA patients into those who were most likely to, and not to, have an RA flare-up at the RA index date. An intuitive approach would

be to select all patients with OS at RA index date and define these people as users of OS at RA index date, but all other patients as non-users of OS at RA index date. However, the problem is complicated by the issue of non-compliance and by the fact that we are seeking to approximate whether or not a patient has a RA flare-up at RA index date. First, a symmetric time window around RA index date is created to define how close each patient's OS prescription is in relation to their RA index date. The boundaries of the time window are denoted as [RA index date $-t$, RA index date $+t$]. We can define eight types of patient with decreasing likelihood of being on OS at RA index date.

- Type A. Patients whose last OS prescription before RA index date overlaps the RA index date window.
- Type B. Patients who had an OS prescription ending in the time window [RA index $-t$, RA index $+t$] and whose first OS after RA index date begins in the window of [RA index, RA index $+2t$]. The fact that they had an OS after RA index indicates that they are likely to have been under more or less continuous OS therapy, although they may not have been fully compliant with their OS therapy before RA index date.
- Type C. Patients who had their first OS prescription after RA index date within [RA index, RA index $+t$]. These patients are not likely to be on OS therapy at RA index date, but a prescription very close to RA index date is likely to indicate a treatment for the flare-up that induced a visit to a doctor at or close to RA index date.
- Type D. Patients whose last OS before RA ends in the interval [RA index $-t$, RA index], but no OS prescription after RA index date falls in [RA index, RA index $+2t$]. This has two competing explanations. Either (i) the patient was under OS therapy but relatively noncompliant, so that the repeat prescription was delayed until after RA index date, or (ii) the patient was compliant, and thus a non-user at RA index date. Unfortunately, we do not have any information to decide between the two.
- Type E. Patients who have OS both before RA and after RA, but not falling in the window [RA index $-t$, RA index $+t$].
- Type F. Patients with no OS prescription after RA index date and whose last OS before RA ends before RA index $-t$.
- Type G patients are those with no OS before RA and whose first OS prescription after RA index date begins in the interval [RA index $+t$, RA index $+2t$].
- Type H. Patients who did not have any OS prescription before or after RA index date. They are surely non-users of OS at RA index date.

Types A, B and C we define as users of OS at RA index date. Types E, F, G and H we define as non-users of OS at RA index date. Finally, type D, the indeterminate patients, are not assigned to either sub-cohort and are excluded from further analyses. Clearly, a critical point is the choice of t , i.e. the length of the time window. It should be long enough to

allow for noncompliance and to correctly classify the new OS users after RA diagnosis. The longer the time window, the more patients are assigned to the sub-cohort of the users of OS at RA index date and the fewer to the sub-cohort of the non-users of OS at RA index date. We decided to choose t to correspond to a noncompliance of OS prescription of 50%, i.e. a patient takes a pill every other day. Descriptive statistics showed that the median scheduled duration of OS prescription is 30 days. Thus, a patient with 50% noncompliance will make their 30-day prescription last 60 days. Thus, t should be 30 days, so the time window should be [RA index date – 30, RA index date + 30]. It is more difficult to establish a time between RA index date and first OS after RA index date short enough to catch patients whose OS prescription is for the RA flare-up at RA index date. In the absence of further information, the choice is 30 days.

Appendix 2

Definition of initiation and cessation of OS therapy

For the sub-cohort of non-users of OS at RA index date the outcome change in inflammation is measured by the first prescription of OS. For the sub-cohort of users of OS at RA index date the outcome is defined as cessation of OS therapy. In practice, this requires the definition of continuous OS therapy. Intuitively, two OS prescriptions P1 and P2 are continuous if the end of P1 corresponds exactly to the date of the prescription of P2 or P2 comes before the end of P1. However, as often patients are not fully compliant with the therapy, they can remain on OS therapy for some time after the end of P1. Hence, in defining continuous OS therapy we chose to allow 45 days' delay, corresponding to noncompliance of 1.5 times the median duration for OS prescription in the Lifelink database. This means that when a patient has a OS of 30 days they are considered on OS therapy until 75 days after the day of the prescription.

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