Anti-rheumatic drug use and risk of hospitalization for congestive heart failure in rheumatoid arthritis

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Objective. To assess the risk of hospitalization for congestive heart failure (CHF) associated with the use of disease-modifying anti-rheumatic drugs (DMARDs) and other medications used in RA.

Methods. We used a case–control design nested within an administrative database cohort of patients with rheumatoid arthritis (RA) who were dispensed a DMARD between September 1998 and December 2001. Subjects identified with a prior history of CHF were excluded. For each hospitalized case of CHF identified during follow-up, 10 controls matched on age and time were randomly selected from the cohort. Conditional logistic regression was used to estimate the rate ratio (RR) of hospitalizations for CHF associated with the current use of specific drugs, adjusted for sex and co-morbidity.

Results. The cohort included 41,885 patients; 75% were women, with an average age at cohort entry of 51 yr. During follow-up, 520 hospitalizations for CHF occurred, for a rate of 10.1 per 1000 per year. The adjusted RR of CHF for current use of any DMARD was 0.7 (95% CI 0.6–0.9) relative to no current use. By DMARD category, there was evidence of a beneficial effect for both tumour necrosis factor-α antagonists (RR 0.5, 95% CI 0.2–0.9) and methotrexate monotherapy (RR 0.8, 95% CI 0.6–1.0). For non-DMARD medications, the rate of CHF was not clearly increased or decreased, except for COX-2 inhibitors. The data suggested an increased risk of CHF with rofecoxib (RR 1.3, 95% CI 1.0–3.1) and a decreased risk of CHF with celecoxib (RR 0.6, 95% CI 0.4, 1.0).

Conclusions. The use of DMARDs was associated with a reduction in the risk of hospitalizations for CHF in this RA cohort. The increased risk with rofecoxib alongside a decreased risk with celecoxib suggests the absence of a class effect with respect to COX-II inhibitors for some types of cardiovascular morbidity.

KEY WORDS: Congestive heart failure, DMARDs, Rheumatoid arthritis.

It is well established that rheumatoid arthritis (RA) is associated with significant morbidity and reduced survival [1, 2]. Cardiac disease is a common cause of death in RA; incidence and mortality rates for coronary artery disease, for example, are much higher among RA patients than the general population [1, 2]. RA can be associated with a host of non-coronary cardiac manifestations; both pericardial and myocardial involvement may be seen [3]. Cardiac events may be related not only to traditional risk factors, such as smoking, diabetes and hypertension [4], but potentially to the disease of RA itself.

Congestive heart failure (CHF) is an important medical complication, associated with high rates of hospitalization and mortality [5]. A recent study has estimated that the rate of CHF is increased almost 2-fold among patients with RA [6]. This study also suggested that RA patients treated with anti-tumour necrosis factor (TNF) therapies were less likely to develop CHF. Though noteworthy, these findings have yet to be replicated. Moreover, evaluations of the risks of CHF after exposures to disease-modifying anti-rheumatic drugs (DMARDs) other than anti-TNF agents, as well as to other medications commonly used in RA, have not been performed. The purpose of this study was to assess the risk of severe episodes of CHF (defined as those requiring hospitalization) associated with the use of DMARDs of all types. We also considered the effect of other medications commonly used in RA.

Patients and methods

The cohort used for this study has been described previously [7]. The cohort subjects came from two North American insurance claims databases: the Protocare longitudinal health benefit claims database (combining data from Medicaid, Medicare, private health maintenance organizations and preferred provider organizations) and the PharMetrics Integrated Outcomes Database (consisting of claims data from over 40 different managed care organizations). Information available from these databases included physician visits, hospitalizations and all prescribed medications dispensed to these individuals, which included over 26 million people at the time these study data were assembled.

For the period between 1 January 1998 and 31 December 2001, we identified all subjects with a diagnosis of RA using the physician billing codes (ICD-9 code 714). The cohort subjects were then further limited to those individuals who were dispensed at least one DMARD after 1 September 1998. Cohort entry was then defined by the date of the first DMARD prescription. These medications...
included methotrexate, hydroxychloroquine, chloroquine, leflunomide, TNF-α antagonists, sulphasalazine, ciclosporin, gold compounds, minocycline, penicillamine, azathioprine and cyclophosphamide. Subjects were all followed from the cohort entry date up to the earliest of four possible events: termination of enrolment in the health plan, outcome of interest, death or end of study period (31 December 2001). The sample was restricted to adults (18 yr or older at cohort entry). Subjects were required to have more than 3 months of eligibility in the health insurance plan prior to cohort entry, and to have no history of CHF at the time of their entry date.

The outcome was the first occurrence of CHF requiring hospitalization during follow-up. These events were identified from all in-patient encounters with an ICD-9 code of 428. Because of the complexity of the time-dependent drug exposures, we used a nested case–control design as a computationally efficient alternative to the cohort approach [8]. For each case of hospitalization for CHF that occurred in the cohort, we selected 10 random controls, matching on age (within 2 yr), month and year of cohort entry, and ensuring that each control was still at risk for a first-time occurrence of CHF on the day the case occurred. Date of CHF hospitalization was designated as the index date for each case–control set. All drugs received during the year prior to the index date were identified from prescription data.

Co-morbidity was identified from diagnoses made prior to the index date, from ICD-9 codes for physician encounters. Prior cardiovascular disease was defined as the diagnosis (based on any physician encounter) of ischaemic heart disease, stroke, peripheral arterial disease and other heart diseases. Other related co-morbid conditions that we considered included those that function as risk factors for ischaemic heart disease: hypertension, diabetes mellitus and hypercholesterolaemia. The remaining additional co-morbid conditions that we adjusted for included respiratory illness, cancer, gastrointestinal disorders and central nervous system disorders.

Data analysis

Person-years of follow-up within the cohort were totalled to estimate the incidence rate of CHF in the cohort. Within the nested case–control sample, we used conditional logistic regression to estimate the rate ratio (RR) of hospitalization for CHF for each of the medication classes. Current exposure to these drugs was defined as a prescription dispensed during the 45-day period prior to the index date.

The DMARDS were analysed as a group and also divided into four categories of time-dependent current use. We defined DMARD exposure categories as: (1) methotrexate monotherapy; (2) leflunomide (with or without other DMARDS); (3) TNF-α antagonists available at the time (etanercept and infliximab) and (4) all other DMARDS (hydroxychloroquine, chloroquine, sulphasalazine, azathioprine, gold compounds, minocycline, ciclosporin, penicillamine, chlorambucil and cyclophosphamide) and any DMARD combinations (including combinations with methotrexate).

Other drugs that we considered included glucocorticoids, traditional non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors. In view of the previous studies suggesting that, among NSAIDs, naproxen may exhibit important cardiovascular effects [9], traditional non-selective NSAIDs were separated into ‘naproxen’ and ‘all others’. COX-2 inhibitors were also separated into rofecoxib and celecoxib (the two COX-2 inhibitors available during this period). All drugs were included in conditional regression models that controlled concurrently for the other medications, as well as for age, sex and duration of time in the cohort, with additional adjustment for co-morbidity.

Results

The cohort included 41,885 individuals who had both a diagnosis of RA and a dispensed DMARD prescription; 33,009 subjects were from the PharMetrics database and 8876 from the Protocare database. The average age at cohort entry was 51 yr; as expected in RA, the majority (75%) were women. The entire RA cohort generated 51,301 person-years of follow-up time during the study interval. During this time, 520 cases of CHF occurred, for an incidence rate of 10.1 events per 1000 person-years. For persons aged 65 or older at cohort entry, the incidence of CHF was 179 events in 6780 person-years, for a rate of 26 events per 1000 person-years. In comparison, data from the Framingham study placed the general population figure for CHF incidence in this age group at less than 10 per 1000 person-years [10].

The mean ages of CHF cases and their matched controls were 67 and 65 yr, respectively (Table 1). Cases occurred, on average, just under a year after cohort entry. Women represented 67% of the cases and 75% of the controls. The cases had considerably more co-morbidity, including cardiovascular disease and risk factors, as well as non-cardiovascular disorders, prior to the index date, justifying inclusion of co-morbidity in the adjusted analyses.

As indicated in Table 2, the adjusted RR for CHF hospitalizations related to current use of any DMARD was 0.7 (95% CI 0.6–0.9), relative to no current use. This effect was suggested consistently for each of the four DMARD categories, with evidence of a beneficial effect for TNF-α antagonists (RR 0.5, 95% CI 0.2–0.9) and methotrexate monotherapy (RR 0.8, 95% CI 0.6–1.0). With respect to the other (non-DMARD) medications commonly used in RA, the rate of CHF was not clearly increased or decreased with the current use of any agent, except for COX-2 inhibitors. Here, interestingly, the data suggested an increased risk of CHF with rofecoxib (RR 1.3, 95% CI 1.0–3.1) and a decreased risk of CHF with celecoxib (RR 0.6, 95% CI 0.4–1.0).

Discussion

We demonstrated, in a large cohort of RA patients, a protective effect of current DMARD exposure against hospitalization for CHF. There are several possible explanations for the results. One may be that the findings represent an indirect consequence of the favourable effects of DMARDs on cardiac risk factors in RA. For example, the ability of DMARDs to improve RA symptoms,
leading to greater physical activity, may have contributed to a decreased risk of hypertension, type 2 diabetes and coronary artery disease, all important determinants of CHF. On the other hand, the effective control by DMARDs of systemic inflammation could potentially lower cardiac risk, though this mechanism remains contentious. Although one may hypothesize that the steroid-sparing effects of DMARDs may reduce cardiovascular risk in RA, we do not believe this explains our study results, as the analyses adjusted for concomitant corticosteroid use.

Our finding of differential effects for COX-2 inhibitors (decreased risk for rofecoxib and increased risk for celecoxib) is interesting. An increased risk of CHF with the use of rofecoxib, but not celecoxib, was suggested in a recent cohort study of an elderly general population sample [11]. Randomized controlled trial data sets have suggested higher rates of adverse effects, including hypertension, peripheral oedema and coronary events, with rofecoxib [12, 13]. It is conceivable that physicians prescribed rofecoxib versus celecoxib differentially according to risk factors for CHF (i.e. were less likely to prescribe rofecoxib in persons at more risk), but in that event we would not expect to see lower RRs for celecoxib.

In the setting of a rare disease (RA) and a relatively rare outcome (CHF), administrative claims databases are extremely useful to conduct analyses with large samples and within a relatively short time frame. Clearly, a major strength of our database study is the large sample size. However, the use of administrative databases also has potential limitations. The database did not permit confirmation of the diagnosis of RA or the outcome of CHF. Regarding the diagnosis of RA, other types of arthritis (especially osteoarthritis, which is relatively common [14]) may be classified as RA if one relies solely on physician diagnostic billing codes. However, use of physician encounter data, combined with a dispensed prescription for a DMARD, optimizes the validity of the RA diagnosis, since DMARDs are essentially excluded from the regular treatment options for OA [13]. Also, the demographics (age and sex distribution) of our study cohort is similar to that reported in clinical RA cohorts [16].

Regarding the use of administrative databases for the outcome ascertainment of CHF, previous work has demonstrated a very high positive predictive value [11, 17]. We examined only CHF cases requiring hospitalization; we acknowledge that not all CHF cases are necessarily hospitalized. However, we wished to look at severe cases of CHF, which led to our decision to examine only those CHF cases that required hospitalization. This reflects the approach adopted in other administrative database studies examining CHF as an outcome [11, 17].

In pharmacoepidemiology studies, an important potential source of bias is ‘channelling’, whereby medication exposure occurs differentially according to pre-existing risk for the outcome event. We considered this possibility and made several attempts to control for it. First of all, since our main exposure of interest was DMARD use, we aimed to study a group that was relatively homogeneous with respect to the likelihood of medication exposure. We thus assembled an RA cohort whose members all had some DMARD exposure history, and looked at their CHF risk with respect to their current DMARD use. We also attempted to exclude those with a history of CHF, and adjusted for all the major co-morbidity that might in some way be associated with both exposure and outcome, including hypertension, diabetes, hyperlipidaemia and other coronary artery disease.

We did consider the possibility that our study may have been subject to residual confounding. The estimates of RR for DMARDs could still reflect a differential prescription by physicians of drugs according to CHF risk factors, if there was error in our measures of co-morbidity. Although one may argue that unmeasured potential confounders (weight, physical activity and smoking) could have affected the results, it seems unlikely that a rheumatologist would prescribe DMARDs selectively according to these variables. DMARD use is currently a cornerstone for all RA patients.

There is another possible bias in pharmacoepidemiological research, which can falsely create an apparent protective effect for current medication exposure. This phenomenon can occur when deteriorating health leads to discontinuation of the drug as well as eventual occurrence of the outcome of interest (the outcome being related to the deteriorating health, not to the pharmacological effect of the drug). That might have occurred in our study, for example, if rheumatologists tended to stop DMARD prescription in individuals who became at risk for CHF, just before the event. Again, this seems unlikely. However, we did examine for this
effect in subjects who discontinued DMARD use, and found no apparent rise in cardiovascular events in the period immediately following drug discontinuation. Thus, we do not believe this phenomenon explains our findings.

We do acknowledge that the time frame of our study is relatively short, since we observed individuals only over a short period (1998–2001). We plan to complete future studies with other databases that will allow longer period of follow-up.

Despite FDA post-marketing surveillance that did not seem to indicate an excess of CHF exacerbations among RA patients treated with TNF-α antagonists, clinicians are still advised to ‘carefully consider the potential risks and benefits of such therapy in RA patients with CHF or risk factors for CHF’ [18]. Our observational finding of a decreased association of CHF with TNF-α antagonists in RA does not address the issue of the effects of these agents in a RA patient with established CHF. We note that our protocol stipulated the exclusion of subjects with a prior history of CHF at the time of their entry date for our study cohort. However, as we relied on physician diagnostic code data from the time of the patients’ enrolment in the insurance database, we may have missed a remote history of CHF in some subjects. In the last two decades, the more aggressive use of DMARDs in RA has increased the possibility of good disease control, and newer agents have been an important development (particularly for patients with intolerance or resistance to methotrexate and other classic DMARDs). The cardiovascular effects of newer DMARDs, specifically TNF-α antagonists, have been a concern, since the data from CHF trials of the anti-TNF-α agents suggested that short-term TNF-α antagonism did not improve CHF; in fact, high-dose TNF-α blockade adversely affected the clinical outcomes (hospitalization or death) of heart failure patients [19]. It is possible that the role of TNF-α in CHF pathogenesis may be quite distinct in different stages of disease (for example, the pre-clinical stage versus the stage of overt heart failure). We do note that since previous data from clinical trials of these agents in existing CHF suggested possible detrimental effects, the drugs should probably continue to be considered relatively contraindicated in individuals with established symptomatic CHF. However, recent work, in addition to ours, has also suggested that RA patients treated with anti-TNF therapies are less likely to develop new-onset CHF [6].

In summary, we demonstrated, in a large cohort of RA patients, a protective effect of current DMARD exposure against CHF. These intriguing results suggest that the benefits of aggressive DMARD therapy in RA may not be limited to the musculoskeletal system.

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