Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 57, No. 7, October 15, 2007, pp 1151–1157
DOI 10.1002/art.23003

ORIGINAL ARTICLE

The Importance of the Disease Process and Disease-Modifying Antirheumatic Drug Treatment in the Development of Septic Arthritis in Patients With Rheumatoid Arthritis

CHRISTOPHER J. EDWARDS,[1] CYRUS COOPER,[1] DAVID FISHER,[2] MAX FIELD,[3] TJEERD P. VAN STAA,[4] AND NIGEL K. ARDEN[1]

Objective. **To evaluate the effect of disease-modifying antirheumatic drugs (DMARDs) on the likelihood of patients with rheumatoid arthritis (RA) developing septic arthritis (SA).**

Methods. **The United Kingdom General Practice Research Database (GPRD) was used to identify adults with RA, and age-, sex-, and practice-matched control subjects. Subjects were studied between 1987 and 2002. The risk of developing SA (excluding infected joint replacements) for individuals with RA was calculated and the effect of DMARD use determined.**

Results. **A total of 136,977 subjects (34,250 patients with RA, 102,747 controls) were identified. SA was identified in 345 subjects, of which 321 (236 in patients with RA, 85 in controls) cases occurred during the study period. The incidence rate of SA was 12.9 times higher in subjects with RA than in those without (95% confidence interval [95% CI] 10.1–16.5, $P < 0.001$). The incident rate ratios (IRRs) for developing SA while receiving DMARDs compared with receiving no DMARDs were different for different medications. Penicillamine (adjusted IRR 2.51, 95% CI 1.29–4.89, $P = 0.004$), sulfasalazine (adjusted IRR 1.74, 95% CI 1.04–2.91, $P = 0.03$), and prednisolone (adjusted IRR 2.94, 95% CI 1.93–4.46, $P < 0.001$) were associated with an increased incidence of SA when compared with not receiving any DMARD. The use of other DMARDs including methotrexate showed no such effect.**

Conclusion. **Individuals with RA have an increased risk of developing SA. This increased risk can be attributed to both the disease process and the use of DMARDs.**

KEY WORDS. Septic arthritis; Rheumatoid arthritis.

INTRODUCTION

Septic arthritis (SA) is a rheumatologic emergency that may cause synovial joint destruction and death. SA is more likely to occur in individuals who are older, have coexistent medical illness (diabetes mellitus, chronic renal failure, chronic cardiac failure), and have preexisting joint damage from arthritis.

Rheumatoid arthritis (RA) is the most common inflammatory arthritis and is associated with high levels of morbidity and a shortened lifespan. Individuals with RA are at particular risk of developing SA (1–4). This may be due to several reasons, such as existing joint disease predisposes to bacterial joint colonization, and RA itself and its treatment with corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and new biologic therapies may produce changes in immune function required for protection from bacterial pathogens. In recent years there has been a change toward early and more aggressive treatment of RA. DMARDs are now used earlier, in higher doses, and often in combination to control disease activity in its early stages. In particular, the use of the DMARD methotrexate has increased in the last 20 years (5). It has been suggested that methotrexate may be associated with an increased

Supported by grants from Proctor & Gamble Pharmaceuticals UK, the Medical Research Council, and the Southampton Rheumatology Trust.

[1]Christopher J. Edwards, MD, FRCP, Cyrus Cooper, MD, FMedSci, Nigel K. Arden, MD, MRCP: University of Southampton, and Southampton General Hospital, Southampton, UK; [2]David Fisher, BSc: University of Southampton, Southampton, UK; [3]Max Field, MD, FRCP: Royal Infirmary, Glasgow, UK; [4]Tjeerd P. van Staa, PhD: University of Southampton, Southampton, UK, and the University of Utrecht, Utrecht, The Netherlands.

Address correspondence to Christopher J. Edwards, MD, FRCP, Department of Rheumatology, Southampton General Hospital, Tremona Road, Southampton, UK SO16 6YD. E-mail: cedwards@soton.ac.uk.

Submitted for publication November 30, 2006; accepted in revised form March 19, 2007.

likelihood of developing SA (4). Although these DMARDs and cytokine-inhibiting biologic therapies are generally believed to be immunosuppressive and likely to increase the incidence of SA, some studies suggest that their use may produce normalization of some aspects of immune function (6). It remains unclear if the increased incidence of SA associated with RA is increased by DMARD use and if this is true for all DMARDs. The increasing use of earlier and more aggressive treatment regimens makes it vital to know what effect this is likely to have on the incidence of important infections such as SA. In this study, we looked at the incidence and associated clinical diseases of SA in patients with RA and the effect of DMARDs on the likelihood of developing SA using the UK General Practice Research Database (GPRD).

PATIENTS AND METHODS

Study population. General practitioners (GPs) in the UK play a key role in the delivery of health care by providing primary care and referral to specialist hospital services. Patients are registered with a single practice that stores medical information from primary care visits and hospital visits. The GPRD comprises all computerized medical records of a sample of patients visiting GPs in the UK (covering a population of more than 7 million men and women from 683 contributing practices). The GPRD records demographic information, prescription data, clinical events, specialist referrals, hospital admissions, and major outcomes (7–13). Data are stored using OXMIS and Read codes for diseases that are cross-referenced to the International Classification of Diseases, Ninth Revision (ICD-9). All entries are internally validated by cross-checking within the practice and by comparisons with external statistics (14). Only practices that pass this quality control are used as part of the GPRD database. Independent validation studies have confirmed a high level of completeness and validity of the diagnostic and prescribing data in the GPRD (5). Deleting or encoding personal and clinic identifiers ensures the confidentiality of information in the GPRD. The GPRD is owned by the UK Department of Health and managed by the UK Medicines Control Agency.

Defining RA and SA cases. Using the GPRD, we identified all patients with a diagnosis of RA (ICD-9 code 714.0) entered into the database between June 1987 and April 2002 from the 3.5 million individuals in the database at that time. Patients were included if RA was diagnosed at any stage during this period. At least 3 control subjects without RA, matched by age (within 5 years), sex, and practice, were defined for each RA case. SA was defined in both the RA and control population using ICD-9 codes, including ICD 710, occurring for the first time during the study period in individuals with RA and controls. Individuals with an infected joint prosthesis were excluded.

Defining DMARD use. DMARD use was defined as at least 1 DMARD prescription for an individual with RA during the study period. DMARD therapy was considered to be continuous if the gap between prescriptions was <14 weeks. The length of individual DMARD use was defined as the time between the first and last prescription of that drug within the previously defined continuous period plus 15 days based on the average prescription lasting 30 days and allowing for patients not to complete the course. A prescription of more than 1 DMARD simultaneously was defined as combination therapy.

Statistical analysis. The prevalence of RA was estimated midyear in 1998 by dividing the total number of patients with a diagnosis of RA by the total number of individuals in the GPRD at that time. The incidence of RA was calculated by dividing the number of new diagnoses of RA in 1998 by the total person-years of followup in 1998. The characteristics of RA cases versus controls were compared using chi-square tests and unpaired *t*-tests.

The relationship of predictor variables to the incidence of SA was analyzed using person-years analysis and Poisson regression. The cumulative amount of time spent by all valid subjects in a certain state (e.g., having RA or heart disease or not, or receiving a DMARD prescription or not) and the number of SA incidences during that time were calculated and expressed as an SA incidence rate per 1,000 person-years. The coefficients obtained from Poisson regressions are incident rate ratios (IRRs), the ratio of the incident rate while in a certain state compared with the incident rate while in a different state. This approach enabled as much information as possible to be obtained from the data set, because subjects could contribute to the analysis throughout their observation period, regardless of what state they were in. The only exception to this approach was for RA itself: here, instead, patients whose first diagnosis of RA was subsequent to their first diagnosis of SA were removed from the analysis along with their matched controls. This not only made the analyses more coherent, but also avoided the possibility of bias from preclinical RA. All analyses were performed using Stata software, version 8.2 (StataCorp, College Station, TX).

RESULTS

Numbers of patients with RA. A total of 34,364 patients with an ICD-9 code for RA were identified along with 103,089 controls (3 per case) matched for age, sex, and GP practice. For the purposes of investigating the causal effect of RA on SA, we removed patients with RA who were first diagnosed subsequent to a diagnosis of SA and their matched controls. This left 34,250 RA cases (97% of 34,364) and 102,747 matched controls, which formed the study population. The median followup period was 7 years, 153 days. The mean age of individuals with RA was 55.6 years and 71.4% were female.

DMARD use. Of the 34,250 patients with RA included in the analysis, 17,030 (50%) individuals were prescribed at least 1 DMARD during the study period and 13,557 (40%) received at least 1 course of oral prednisolone; 4,908 (36%) of these 13,557 were not prescribed a DMARD. The

Table 1. Baseline characteristics of RA cases and controls*

Characteristic	Controls (n = 102,747)	RA cases (n = 34,250)	*P*
Female sex	71.4	71.4	1.0
Age, mean years†	55.3	55.6	0.001
BMI, median (IQR) kg/m²‡	25.2 (22.7–28.2)	24.9 (22.3–28.0)	< 0.001
Smoking (ever vs never)	37.5	41.6	< 0.001
Diabetes§	5.55	5.50	0.7
Hypertension§	23.5	22.8	0.01
Heart failure§	6.39	9.38	< 0.001
Renal failure§	0.86	1.83	< 0.001

* Values are the percentage unless otherwise indicated. RA = rheumatoid arthritis; BMI = body mass index; IQR = interquartile range.
† At time of entry into the General Practice Research Database study.
‡ For 68,811 (67%) controls and 23,575 (69%) RA patients.
§ Total proportion, regardless of whether the disease developed before or after RA or SA.

most commonly prescribed DMARD over the entire study period was sulfasalazine (received by 59.7% of the 17,030 individuals prescribed a DMARD) and then methotrexate (40.2%).

Characteristics of the study populations. The RA cases and controls were matched for age and sex and had similar body mass index, smoking history, diabetes mellitus (DM), and hypertension (Table 1). The RA group contained more smokers (41.6% versus 37.5%; $P < 0.001$), and patients with RA were more likely to have heart failure (9.38% versus 6.39%; $P < 0.001$) and renal failure (1.83% versus 0.86%; $P < 0.001$).

Incidence of SA. Data from the middle of the study period were more likely to produce an accurate estimate of incidence of SA and therefore the middle 5 years (1992–1997) of the study period were used. This showed an SA incidence of 0.29 (95% confidence interval [95% CI] 0.27–0.31) per 1,000 person-years for the entire population studied (including RA cases and controls) and 0.11 (95% CI 0.09–0.12) per 1,000 person-years for the control population. In the RA population, the SA incidence was increased at 1.31 (95% CI 1.22–1.41) per 1,000 person-years.

For patients with incident RA (i.e., a first diagnosis of RA during the study period), the incidence of SA was calculated in blocks of 1 year, centered on the time of RA diagnosis. For this analysis, all RA cases and controls were used (n = 34,364 and n = 103,089, respectively) so that SA incidence both before and after RA diagnosis could be studied. Because this analysis was purely exploratory, preclinical RA among yet-to-be-diagnosed cases was not considered to be an issue. The fit from a Poisson model is shown in Figure 1 (IRR 1.06 per year, 95% CI 1.00–1.12, $P = 0.038$). The SA incidence rate appeared to increase steadily with time, both before and after the RA diagnosis. When further adjusted for the age of the subject (categorized as <45 years, 45–60 years, 60–70 years, and ≥70 years), the trend became nonsignificant (relative risk [RR] 1.05, 95% CI 0.99–1.11, $P = 0.10$); much more of the variation was explained by increasing age (IRR 1.37, 95% CI 1.15–1.63, $P < 0.001$) than by time to or from RA diagnosis.

RR for RA versus normal controls. There were 348 identified cases of SA among the 136,997 subjects (34,250 patients with RA and 102,747 matched controls), 321 of which occurred during the study period. Of these, 236 occurred in patients with RA. The incidence rate of SA was 12.9 times greater among patients with RA than among RA controls (95% CI 10.1–16.5, $P < 0.001$).

Risk factors (DM, chronic renal failure, congestive heart failure). A number of chronic medical conditions are known risk factors for the development of SA (Table 2). A diagnosis of RA, hypertension, heart failure, or renal failure significantly increased the risk of future SA, and the incidence of SA was significantly higher while experiencing one or more of these risk factors than while not. Diabetes had a similar, but smaller and nonsignificant effect. Age and smoking status were also investigated as risk factors. Smoking did not predict SA, but the risk of developing SA was found to significantly increase with age (Table 2).

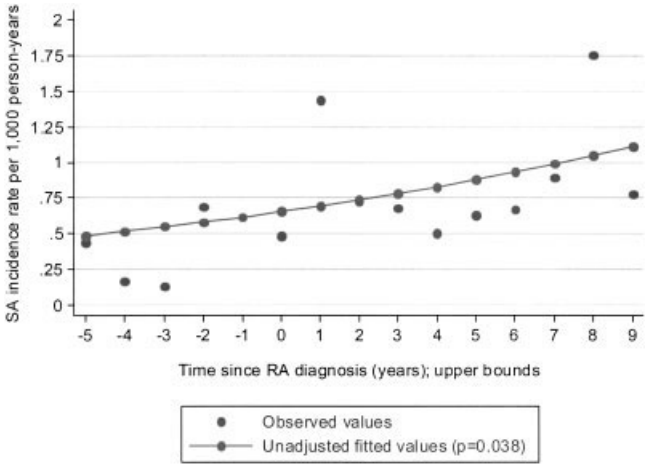

Figure 1. The fit from a Poisson model (incident rate ratio 1.06, 95% confidence interval 1.00–1.12, $P = 0.038$). The septic arthritis (SA) incidence rate appears to increase steadily with time, both as the rheumatoid arthritis (RA) diagnosis approaches and afterward.

Table 2. Univariate Poisson regressions giving independent incidence rate ratios (IRRs) for SA while in the presence (compared with the absence) of potential predictors*

Variable	IRR for SA	95% CI	*P*
RA	12.9	(10.1–16.5)	< 0.001
Diabetes	1.52	(0.95–2.45)	0.08
Hypertension	1.51	(1.17–1.94)	0.001
Heart failure	3.23	(2.26–4.64)	< 0.001
Renal failure	9.47	(5.32–16.9)	< 0.001
Smoking status	0.84	(0.66–1.08)	0.17
Compared with age <45 years†			
Age 45–<60 years	2.58	(1.65–4.04)	< 0.001
Age 60–<70 years	4.13	(2.66–6.40)	< 0.001
Age ≥70 years	3.96	(2.56–6.12)	< 0.001

* SA = septic arthritis; 95% CI = 95% confidence interval; RA = rheumatoid arthritis.
† Linear trend across categories: $P < 0.001$.

Effect of DMARDs on likelihood of developing SA. Of the 236 cases of SA occurring in patients with RA (subsequent to the first diagnosis of RA), the majority were treated with a DMARD or prednisolone during the study period (90%, n = 212). However, this fell to 80% (n = 189) when prescriptions were restricted to those prior to the diagnosis of SA, and only approximately two-thirds (68%, n = 160) were treated with a DMARD or prednisolone in the 2 months immediately prior to the diagnosis of SA. Analysis of the effect of DMARD and prednisolone therapy on the likelihood of individuals with RA developing SA was performed using Poisson regression. This calculated the IRR of SA per 1,000 person-years while receiving a particular DMARD or prednisolone compared with not receiving that drug. The SA incidence rate while receiving a DMARD or prednisolone was 2.17 (95% CI 1.68–2.80, $P < 0.001$) times greater than while receiving no drugs, even after adjustment for RA.

We looked at the effect of DMARDs in the RA case and control populations separately to confirm that this effect was independent of the effect of RA. The incident rate for SA in patients with RA receiving DMARDs was 2.14 (95% CI 1.64–2.78, $P < 0.001$) times greater than in patients with RA not receiving DMARDs, and the corresponding rate ratio for RA controls was 2.80 (95% CI 1.03–7.64, $P = 0.045$).

The effects of individual drugs can be looked at in 2 different ways: the effect of receiving each drug or combination of drugs can be compared with receiving no drug at all, or receiving each drug can be compared with not receiving that drug. In both cases, the results obtained from restricting analyses to the time patients spent with RA were very similar to those obtained by not restricting and adjusting for RA; therefore, the former results are presented (Table 3). Both approaches suggest that receiving either penicillamine or prednisolone, or both, significantly increases the incident rate of SA, even after adjustment for other risk factors. The results also suggest that sulfasalazine and combination therapies also increase the incident rate. However, a post-estimation Wald's test for the hypothesis that the effects of all the drugs are equivalent was nonsignificant ($P = 0.30$). There is great variation

Table 3. IRRs for SA while on a particular disease-modifying antirheumatic drug (DMARD) compared with the incidence on no DMARD using Poisson regression, among RA cases only*

Therapy	IRR	*P*	95% CI	Observation time (person-years)	No. of SA events
Auranofin only	0.00	0.99	NA	432	0
Azathioprine only	1.99	0.34	(0.49–8.14)	1,130	2
Cyclophosphamide only	0.00	0.99	NA	29	0
Cyclosporin only	0.00	0.99	NA	95	0
Hydroxychloroquine only	0.59	0.60	(0.08–4.25)	2,094	1
Leflunomide only	0.00	0.99	NA	60	0
Methotrexate only	1.01	0.98	(0.44–2.34)	7,022	6
Penicillamine only	2.51	0.007	(1.29–4.89)	4,739	10
Sodium aurothiomalate (gold) only	0.00	0.99	NA	2,994	0
Sulfasalazine only	1.74	0.03	(1.04–2.91)	13,469	19
Prednisolone only	2.94	< 0.001	(1.93–4.46)	13,132	36
Any combination	2.50	< 0.001	(1.64–3.81)	15,038	33

* Restricted to time patient spent with RA (before incidence of SA if it occurs). Adjusted for diabetes mellitus, hypertension, renal failure, heart failure, smoking status, and age category. Post-estimation Wald's test for the hypothesis that the effects of all the drugs are equivalent (excluding cyclophosphamide, cyclosporin, infliximab, and leflunomide, because they have very low observation times): χ^2 (8df) = 9.59, $P = 0.30$. NA = not applicable; see Table 2 for additional definitions.

in the length of time spent receiving different drugs, and those drugs that are significant predictors of SA incidence are among the most frequently taken; therefore, it is likely that the significant results are due simply to the larger standard errors associated with these drugs. In any case, it is clear that RA itself is a far more important predictor of SA than any individual drug.

DISCUSSION

Individuals with RA had a significantly greater risk of developing SA than controls that was present before the clinical diagnosis and increased with duration of disease. The majority of individuals with an established diagnosis of RA who developed SA were prescribed a DMARD or prednisolone at some point during the study period (90%); however, only half were taking a DMARD or prednisolone in the 2 months prior to the diagnosis of SA. There was a significantly increased risk of SA in individuals with RA prescribed DMARDs compared with individuals with RA not prescribed DMARDs. Although individuals prescribed DMARDs may be more likely to develop SA, it appeared that not all DMARDs had the same effect. The incidence of SA appeared greater during treatment with penicillamine, sulfasalazine, prednisolone, or any combination compared with no drug. We excluded individuals with an infected prosthesis from this analysis. Therefore, we are unable to comment on the effect of RA on infections of joint prostheses. The number of infected prostheses in this cohort was too small to allow statistical analysis.

Our study provides information on SA in a large number of patients with RA identified from a primary care database in the UK. This database has been used previously to describe DMARD use for RA in the UK (12,13). Patients with RA were identified from primary care records of attendance. In the UK, the GP is the first port of call for all health care, including referral to secondary and tertiary care. For this reason the population studied will include most individuals with RA including those being cared for solely by the GP and those attending secondary care. The prescribing of medication is generally performed by GPs, making it unlikely that DMARD prescribing has been missed. The diagnosis of RA and SA was recorded in a pragmatic manner by GPs in the patient notes. Expert coders then determined the ICD-9 coded diagnosis. Defined clinical classification criteria were not used. The data included in the GPRD have been extensively cross-checked and validated for accuracy (12). The reliability of the diagnosis of RA and other connective tissue diseases in the GPRD is currently being investigated. However, studies of osteoporosis have demonstrated that specificity for the diagnosis of chronic diseases is very high but sensitivity is low (15). Thus, the diagnosis of RA and SA in this data set would be expected to include definite cases but may miss mild or uncertain cases. In addition to diseases such as osteoporosis, the database has also been validated for diagnoses of other inflammatory diseases that are similar to RA such as inflammatory bowel disease (1). The RA population in this study has a sex distribution and mean age consistent with other published populations of patients with RA.

One difficulty in interpreting these results is the lack of disease activity/severity data that are available. For example, individuals with the most aggressive disease may be the ones most likely to be receiving prednisolone and non–first-line DMARDs such as cyclophosphamide and cyclosporin. If severity of RA was the key determinant of SA, then it might appear that these individuals had SA secondary to their DMARD when it was really secondary to disease activity. However, individuals with RA had significantly more hypertension, heart failure, and renal failure, suggesting severe disease with systemic consequences. In addition, our data do not include dosing schedules and those individuals receiving DMARDs may have been receiving only low doses with a weak immunosuppressive effect.

A number of groups have reported an association between SA and RA (2–4,16–18). SA in individuals with RA is particularly important because of its poor prognosis and often atypical presentation. The development of a hot painful joint in an individual with RA is usually assumed to be a flare of RA and its significance is not appreciated. The presentation is also more likely to be polyarticular, which might initially reinforce the feeling that this is a flare of RA (1). This may account for the diagnosis often being made late in the SA course, which may in part account for the poor prognosis of this group. In addition, patients with RA may present late because they often have a normal temperature and white cell count at presentation (4).

The use of immunosuppressive drugs has been suggested as a cause of increased SA (1). However, not all individuals with RA who develop SA are receiving immunosuppressive therapies (19). This may support the idea that the immune dysfunction associated with RA and the coexistent joint damage are more important risk factors than the immunomodulatory therapies that are frequently used. This is supported by our results that demonstrate an increase in the incidence of SA in the months prior to a diagnosis of RA and by the fact that a number of individuals with RA developed SA without receiving DMARDs.

Why could there be a difference in the likelihood of developing SA with different DMARDs? Some DMARDs, such as hydroxychloroquine, are perceived to produce minimal changes in immune function, whereas others, such as cyclophosphamide, are potent immunosuppressive agents. A Cochrane review of cyclophosphamide use for RA demonstrated a high rate of withdrawal due to side effects including increased infections (1,20). Methotrexate has become a commonly used first-line DMARD for the treatment of RA over the last 20 years in the US and the last 10 years in the UK. In clinical practice, recurrent infections associated with methotrexate use occur but are rarely a significant problem. However, there are a number of individual case reports and small series reports of methotrexate use associated with infectious complication. There are also SA cases associated with methotrexate treatment for RA (4,18,20,21). These have included opportunistic organisms such as *Listeria monocytogenes* (22). Other DMARDs have also been associated with SA, including fungal arthritis associated with cyclosporin (23–32). Prednisolone is associated with infections with many or-

ganisms. However, there is little published evidence of an association between corticosteroid use and SA. There is also little evidence for penicillamine or gold therapy. Treatment with both etanercept and infliximab has been associated with SA in persons with RA (25). However, our data set does not allow this association to be explored because there are only limited data available at the start of anti–tumor necrosis factor (anti-TNF) use. Interestingly, the combination of anti-TNF therapy with methotrexate has been associated with increased nasal carriage of *Staphylococcus aureus*, the most common organism implicated in SA. Perhaps the mechanism of action of the DMARD is important. Corticosteroids have multiple actions on the immune system including effects on neutrophil function (6). In our study, the fact that methotrexate had no effect on the likelihood of developing SA may reflect the fact that any increased risk from immunosuppression is cancelled out by the decreased risk associated with more normal immune function and reduced synovial inflammation. Inflammation within the joint may make localization of bacteria following transient bacteremia to the joint more likely. This might also suggest that control of inflammation with effective DMARDs might then reduce the risk again. Further analysis of our data has suggested that there may be no significant difference in the risk of developing SA while receiving different DMARDs. However, different DMARDs had been used by different numbers of individuals for different periods and direct statistical comparison was difficult.

This study demonstrates that having RA increases the likelihood of developing SA considerably. However, it is still an uncommon event. It appears that the presence of RA is perhaps more important than the presence of DMARDs. However, it reinforces the concerns associated with oral corticosteroids and infection in general. Since the introduction of anti-TNF therapies, the use of oral cyclophosphamide in the treatment of RA has reduced considerably. The results are reassuring because they suggest that the most commonly used DMARD, methotrexate, is not associated with increased SA.

This is the largest series of SA cases in RA published to date, and one strength is that it came from a national database without the inherent bias seen in data from a single center. This study demonstrated that individuals with a clinical diagnosis of RA are at an increased risk of developing SA. Use of DMARDs as a group may increase this risk. However, this appears to be different for individual DMARDs and prednisolone. This finding is reassuring as we continue to treat patients with RA who fall into a poor prognostic group more aggressively with DMARDs and prednisolone. However, our finding underlines the possibility of infectious side effects with potent immunosuppressives. Other studies have demonstrated that even powerful immunosuppressive cytokine inhibitors may improve immune functioning.

Interestingly, the increase in the incidence of SA began before the time of RA diagnosis. This result could be due to 2 major reasons. The first is a selection bias created by individuals with early RA attending their GP with a swollen painful joint and being misdiagnosed as having SA. This is less likely to occur the other way around because a definite SA would become worse until hospital admission was required and a more firm diagnosis made. This potential bias would be expected to be greatest prior to a diagnosis of RA. However, the increased incidence of SA continues to increase.

This work suggests that individuals with RA are at increased risk of SA, particularly around the time of diagnosis of RA. However, the increasingly aggressive use of DMARDs such as methotrexate is unlikely to produce a major increase in SA in these individuals.

ACKNOWLEDGMENTS

We are grateful to Ms Vanessa Cox and the computing staff at the Medical Research Council Epidemiology Resource Centre for their assistance in preparation of the data. We are also grateful to Mrs. Pam Freeman for help in preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Dr. Edwards had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Edwards, Cooper, Field, Arden.

Acquisition of data. Edwards, Cooper, van Staa.

Analysis and interpretation of data. Edwards, Cooper, Fisher, van Staa, Arden.

Manuscript preparation. Edwards, Cooper, Field, van Staa, Arden.

Statistical analysis. Edwards, Fisher, Arden.

ROLE OF THE STUDY SPONSOR

Proctor and Gamble provided financial support to purchase the General Practice Research Database using an unrestricted educational grant. However, they had no role in the study design, data collection, data analysis, or writing of the manuscript.

REFERENCES

1. Edwards CJ, Arden NK, Fisher D, Saperia JC, Reading I, van Staa TP, et al. The changing use of disease-modifying antirheumatic drugs in individuals with rheumatoid arthritis from the United Kingdom General Practice Research Database. Rheumatology (Oxford) 2005;44:1394–8.
2. Rahman MM, Leong KP, Edwards CJ, Chng HH. Five-and-a-half year study of 107 patients with septic arthritis in a general hospital in Singapore. APLAR Journal of Rheumatology 2003;6:10–5.
3. Cooper C, Cawley MI. Bacterial arthritis in an English health district: a 10 year review. Ann Rheum Dis 1986;45:458–63.
4. Kaandorp CJ, van Schaardenburg D, Krijnen P, Habbema JD, van de Laar MA. Risk factors for septic arthritis in patients with joint disease: a prospective study. Arthritis Rheum 1995; 38:1819–25.
5. Gupta MN, Sturrock RD, Field M. A prospective 2-year study of 75 patients with adult-onset septic arthritis. Rheumatology (Oxford) 2001;40:24–30.
6. Ehrenstein MR, Evans JG, Singh A, Moore S, Warnes G, Isenberg DA, et al. Compromised function of regulatory T cells in rheumatoid arthritis and reversal by anti-TNF-alpha therapy. J Exp Med 2004;200:277–85.
7. The general practice research database: information for researchers. London: Office for National Statistics; 1996.
8. Hall G. Pharmacoepidemiology using a UK database of primary care records. Pharmacoepidemiol Drug Saf 1992;1:33–7.
9. Hollowell J. General practice research database (GPRD): scope

and quality of data. London: Office of Population Censuses and Statistics; 1994.
10. Lis Y, Mann RD. The VAMP research multi-purpose database in the UK. J Clin Epidemiol 1995;48:431–43.
11. Mann RD, Hall G, Chukwujindu J. Research implications of computerised primary care. Post Marketing Surveillance 1992;5:259–69.
12. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology (Oxford) 2000;39: 1383–9.
13. Walley T, Mantgani A. The UK General Practice Research Database. Lancet 1997;350:1097–9.
14. Van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HG. The use of a large pharmacoepidemiological database to exposure to oral corticosteroids and risk of fractures: validation of study population and results. Pharmacoepidemiol Drug Saf 2000;9:359–66.
15. Lewis JD, Brensinger C, Bilker WB, Strom BL. Validity and completeness of the General Practice Research Database for studies of inflammatory bowel disease. Pharmacoepidemiol Drug Saf 2002;11:211–8.
16. Ryan MJ, Kavanagh R, Wall PG, Hazleman BL. Bacterial joint infections in England and Wales: analysis of bacterial isolates over a four year period. Br J Rheumatol 1997;36:370–3.
17. Kaandorp CJ, Krijnen P, Moens HJ, Habbema JD, van Schaardenburg D. The outcome of bacterial arthritis: a prospective community-based study. Arthritis Rheum 1997;40:884–92.
18. Kaandorp CJ, Dinant HJ, van de Laar MA, Moens HJ, Prins AP, Dijkmans BA. Incidence and sources of native and prosthetic joint infection: a community based prospective survey. Ann Rheum Dis 1997;5:470–5.
19. Suarez-Almazor ME, Belseck E, Shea B, Wells G, Tugwell P. Cyclophosphamide for treating rheumatoid arthritis. Cochrane Database Syst Rev 2000;4:CD001157.
20. Jansen TL, van Heereveld HA, Laan RF, Barrera P, van de Putte LB. Septic arthritis with Listeria monocytogenes during low-dose methotrexate. J Intern Med 1998;244:87–90.
21. Jobanputra P, Maggs F, Homer D, Bevan J. Monitoring and assessing the safety of disease-modifying antirheumatic drugs: a West Midlands experience. Drug Saf 2002;25:1099–105.
22. Cassuto-Viguier E, Mondain JR, van Elslande EL, Bendini JC, Gaid H, Franco M, et al. Fatal outcome of Aspergillus fumigatus arthritis in a renal transplant recipient. Transplant Proc 1995;2:2461.
23. Amital H, Aamar S, Rubinow A. Bilateral septic arthritis of the hip: does etanercept play a role? A case report. J Bone Joint Surg Am 2003;85:2205–6.
24. Baghai M, Osmon DR, Wolk DM, Wold LE, Haidukewych GJ, Matteson EL. Fatal sepsis in a patient with rheumatoid arthritis treated with etanercept. Mayo Clin Proc 2001;76:653–6.
25. Bassetti S, Wasmer S, Hasler P, Vogt T, Nogarth D, Frei R, et al. Staphylococcus aureus in patients with rheumatoid arthritis under conventional and anti-tumor necrosis factor-alpha treatment. J Rheumatol 2005;32:2125–9.
26. Elwood RL, Pelszynski MM, Corman LI. Multifocal septic arthritis and osteomyelitis caused by group A Streptococcus in a patient receiving immunomodulating therapy with etanercept. Pediatr Infect Dis J 2003;22:286–8.
27. Katsarolis I, Tsiodras S, Panagopoulos P, Giannitsioti E, Skarantavos G, Ioannidis T, et al. Septic arthritis due to Salmonella enteritidis associated with infliximab use. Scand J Infect Dis 2005;37:304–5.
28. Kaur PP, Derk CT, Chatterji M, Dehoratius RJ. Septic arthritis caused by Actinobacillus ureae in a patient with rheumatoid arthritis receiving anti-tumor necrosis factor-alpha therapy. J Rheumatol 2004;31:1663–5.
29. Nadarajah K, Pritchard C. Listeria monocytogenes septic arthritis in a patient treated with etanercept for rheumatoid arthritis. J Clin Rheumatol 2005;11:120–2.
30. Olivieri I, Padula A, Armignacco L, Sabatella V, Mancino M. Septic arthritis caused by Moraxella catarrhalis associated with infliximab treatment in a patient with undifferentiated spondarthritis. Ann Rheum Dis 2004;63:105–6.
31. Rachapalli S, O'Daunt S. Septic arthritis due to Listeria monocytogenes in a patient receiving etanercept [letter]. Arthritis Rheum 2005;52:987.
32. Schett G, Herak P, Graninger W, Smolen JS, Aringer M. Listeria-associated arthritis in a patient undergoing etanercept therapy: case report and review of the literature. J Clin Microbiol 2005;43:2537–41.