The Association of Rheumatoid Arthritis and Its Treatment with Sinus Disease

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ABSTRACT. ***Objective.*** To determine if rates of sinus disease are increased in patients with rheumatoid arthritis (RA) and whether RA treatment alters the risk of sinus disease.

Methods. As part of a longitudinal study of rheumatic disease outcomes, 7,243 patients with RA, 1,667 with osteoarthritis (OA), and 447 with fibromyalgia (FM) were evaluated for important sinus problems in 2003. We defined an important sinus problem as one that required a physician visit.

Results. The lifetime prevalence of sinus disorders among all patients was 42.9%. During the previous 6 months 22.3% of patients with RA, 23.9% with OA, and 25.1% with FM visited a physician for a sinus problem and 22.4%, 23.9%, and 25.1% , respectively, received a prescription medication for a sinus problem. After adjustment for age and sex, the rate of physician visits for a sinus problem was significantly lower for patients with RA (22.1%) compared to patients with OA (24.8%). The strongest predictor of sinus problems among all patients was a history of allergy or asthma. Sinus problems were more common among users of etanercept: odds ratio (OR) 1.2; 95% confidence interval (CI): 1.0-1.4 univariably, and OR 1.2; 95% CI: 1.0-1.4 multivariably. Sulfasalazine (OR 0.7; 95% CI: 0.5-0.9) and leflunomide (OR 0.8; 95% CI: 0.7-1.0) had a protective effect on sinus problems.

Conclusions. Sinus problems are decreased in patients with RA compared to OA and FM. Slight protective effects on sinus problems are noted with sulfasalazine and leflunomide, and a slight increase in risk of sinus problems is noted with etanercept. (J Rheumatol 2006;33:2412–5)

Key Indexing Terms:
SINUSITIS RHEUMATOID ARTHRITIS SULFASALAZINE
ANTI-TUMOR NECROSIS FACTOR THERAPY LEFLUNOMIDE

Sinus problems, whose common symptoms include fatigue and increased pain[1,2], are common in the general population and may be increased in patients with immune disorders[3,4]. In addition, clinical trials suggest an increase in sinus symptoms in patients with rheumatoid arthritis (RA) treated with anti–tumor necrosis factor (TNF)[5]. Despite these data, there have been no studies of sinus disease in RA.

We became interested in sinusitis in the context of anti-TNF therapy in the clinic when some patients receiving anti-TNF therapy reported an increase in the number and severity of sinus exacerbations. This, in turn, raised the question as to whether RA, in and of itself, was associated with an increased rate of sinus problems.

Sinus disease has been difficult to define[6], and is associated with and overlaps with upper respiratory illness (colds), allergic disease, and fungal and bacterial infections.

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We had several aims: (1) to determine the rate of sinus problems and whether they occurred more frequently in patients with RA; (2) to determine which clinical symptoms were associated with sinus problems; (3) to determine if anti-TNF therapy or other disease modifying antirheumatic drug (DMARD) therapy was associated with sinus problems; and (4) to determine the incidence rate of hospitalization for sinus disease in patients with RA.

MATERIALS AND METHODS

Patient sample and assessments. Patients in this study were participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of RA outcomes. Patients are recruited from the practices of US rheumatologists and are followed with semi-annual questionnaires. The methods and characteristics of the NDB have been described[7-11]. NDB participants are asked to complete semi-annual, detailed 28-page questionnaires about all aspects of their illness. At each assessment, demographic variables are recorded including sex, age, ethnic origin, education level, current marital status, and medical history. Disease status and activity variables collected include the Stanford Health Assessment Questionnaire functional disability index (HAQ)[12,13] and visual analog scales (VAS) for pain and fatigue[14]. In addition, patients report all drugs used and all hospitalizations during each 6-month period.

Our study comprised 9,357 patients with RA, osteoarthritis (OA), or fibromyalgia (FM) who completed a questionnaire in December 2003 that included questions related to sinus problems. In this questionnaire we asked patients if during the last 6 months they had: (1) used over-the-counter medications for a sinus problem, (2) used medications for a sinus problem prescribed by a physician, and (3) consulted a physician specifically because of a sinus problem during this period. For the purposes of this study we operationally defined a sinus problem as being present if patients specifically consulted a physician because of the sinus problem. We also obtained lifetime

history of sinus problems, using the following question: "Were you ever told by a physician that you had sinus problems?"

To compute incidence rates for sinus hospitalization in RA, we also studied 13,682 patients with RA who participated in the NDB from 1999 through 2003. Our case definition of sinus hospitalization included ICD9 codes 461-461.9 and 473-473.9.

Statistical methods. Differences between groups for sinus related problems in Table 1 were assessed by logistic regression, adjusted for age and sex. Univariable and multivariable associations between sinus problems and predictor variables (Tables 2 and 3) were assessed with logistic regression. Incidence rates for sinus hospitalization counted only the first hospitalization for each patient. Poisson confidence intervals (CI) were used, and statistical computations were performed using Stata (College Station, TX, USA) version 8.2[15].

RESULTS

Table 1 presents rates of consultations for sinus problems and use of sinus medication over the last 6 months. The lifetime prevalence of sinus disorders among all study subjects was 42.9%. Adjusted for age and sex, patients with RA were less likely to consult a physician for a sinus problem or to use prescription or non-prescription sinus medications compared to non-RA patients. In addition, they were less likely to report sinus problems over their lifetime. Almost 29% of patients with RA used a prescription or non-prescription sinus medication during the previous 6 months. Among patients with RA, 22.4% consulted a physician for sinus problems and 40.3% identified sinus problems occurring over their lifetimes. Differences between patients with RA and OA were significant at the 0.05 level except for over-the-counter medications. Differences between patients with FM and those without, adjusted for age and sex, were significant ($p < 0.05$) only for lifetime sinus problems. Overall, these data show that sinus problems and sinus medication use is not increased in RA.

Among patients with RA, sinus problems were more common in younger patients and in women (Table 2), adjusted for sex and age, respectively. Adjusted for age and sex, the strongest correlates of sinus problems in RA were allergies [odds ratio (OR) 2.27; 95% CI: 2.01–2.57] and asthma (OR 1.64; 95% CI: 1.43–1.89). Sinus problems were also associated with severity of RA (Table 2), as measured by HAQ, pain, fatigue, and FM survey criteria[16]. Among treatment variables, leflunomide (OR 0.83; 95% CI: 0.71–0.99) and sulfasalazine (OR 0.62; 95% CI: 0.47–0.82) had a protective effect. The risk of sinus problems was increased in those using etanercept (OR 1.21; 95% CI: 1.04–1.41).

To evaluate treatment effect in a multivariable environment, we regressed sinus problem simultaneously on all of the variables of Table 2, as shown in Table 3. Etanercept (OR 1.21; 95% CI: 1.02–1.4) was associated with increased risk of sinus problems. Sulfasalazine (OR 0.68; 95% CI: 0.51–0.90) and leflunomide (OR 0.84; 95% CI: 0.70–0.99) were associated with reduced risk of sinus problems. We tested whether the coefficients were different between etanercept and other anti-TNF treatments. Results showed that the risk of sinus problems was greater among those receiving etanercept versus infliximab (OR 1.20; 95% CI: 1.00–1.45) and no statistical difference for etanercept versus adalimumab (OR 1.11; 95% CI: 0.77–1.59).

We also studied the incidence and prevalence of hospitalization for sinus disease or surgery in the RA group. Of 13,682 patients with RA seen from 1999 through 2003, the prevalence of hospitalization was 4.01 per 10,000 patients (95% CI: 2.21–5.82) and the incidence rate through 122,381 patient-years of exposure was 1.55 (95% CI: 0.93–2.42) per 10,000 patient-years. When stratified by sex, the rates were 2.66 (95% CI: 1.07–5.48) for men and 1.25 (95% CI: 0.65–2.18) for women per 10,000 patient-years of exposure.

DISCUSSION

Data from the third National Health and Nutrition Examination Survey, 1988-1994 (NHANES) indicated that 25% of the adult population reported having sinusitis or sinus problems at least once during the previous 12 months[17], an estimate consistent with the 6-month prevalence of sinus problems in the current study (22.8%). Chronic sinusitis is less common, with annual estimates of 14.1% from NHANES[18] and between 5.7% in women and 3.4% in men in Canada[19]. Recently, using rigorous methodology, researchers from the Mayo Clinic group reported the annual age and sex

Table 1. Sinus problems and medication use in patients with RA, OA, and FM. Results are expressed as percentage (95% confidence interval).

Diagnosis Group (n)	Sinus Problems in Last 6 mo	Sinus Problems in Lifetime	OTC Sinus Medications	Prescription Sinus Medications
Crude estimates				
RA (7,243)	22.4 (21.4, 23.3)	40.3 (39.2, 41.5)	28.6 (27.6, 29.7)	28.9 (27.8, 29.9)
OA (1,667)	24.0 (21.9, 26.0)	48.6 (46.2, 51.0)	27.8 (25.7, 30.0)	30.7 (28.5, 32.9)
FM (447)	25.1 (21.0, 29.1)	63.2 (58.7, 67.7)	37.4 (32.9, 41.9)	35.3 (30.9, 39.8)
Adjusted estimates*				
RA (7,243)	22.1 (21.1, 23.0)	40.2 (39.1, 41.4)	27.8 (26.8, 28.9)	28.6 (27.3, 29.4)
OA (1,667)	24.8 (22.7, 26.9)	49.3 (46.8, 51.8)	29.7 (27.4, 32.0)	31.9 (29.6, 34.2)
FM (447)	22.0 (18.5, 26.0)	59.3 (54.4, 63.9)	32.3 (28.1, 36.7)	30.9 (26.8, 35.3)
RA vs non-RA, p	0.050	< 0.001	0.033	0.004

* Adjusted for age and sex. OTC: over-the-counter.

Table 2. Associations of sinus problems with demographic and clinical variables during the last 6 months in patients with RA (n = 7,243). Odds ratios (OR) are from separate regression analyses for each variable in column one, adjusting for age and sex, except for age and sex, which are adjusted for sex and age, respectively.

Variable	Mean (SD)/Percent	OR (95% CI)
Age, yrs	62.2 (12.4)	0.98 (0.98, 0.99)*
Sex, % male	21.5	0.78 (0.68, 0.89)*
Non-Hispanic White, %	92.7	1.24 (0.99, 1.56)
Education, yrs	13.6 (2.31)	1.02 (0.99, 1.05)
MTX, %	57.5	0.98 (0.87, 1.10)
Prednisone, %	34.1	1.00 (0.89, 1.13)
Infliximab, %	31.9	0.92 (0.82, 1.04)
Hydroxychloroquine, %	19.0	1.03 (0.90, 1.19)
Leflunomide, %	14.6	0.83 (0.71, 0.99)*
Etanercept, %	14.5	1.21 (1.04, 1.41)*
Adalimumab, %	3.0	1.16 (0.85, 1.58)
Sulfasalazine, %	5.8	0.62 (0.47, 0.82)*
Fatigue, 0–10	4.2 (2.87)	1.07 (1.05, 1.09)*
Pain, 0–10	3.5 (2.68)	1.05 (1.03, 1.07)*
HAQ, 0–3	1.03 (0.72)	1.15 (1.07, 1.25)*
Allergies ever, %	22.7	2.27 (2.01, 2.57)*
Asthma ever, %	16.0	1.64 (1.43, 1.89)*
Fibromyalgia (survey criteria), %	15.8	1.16 (1.39, 1.85)*

* $p < 0.05$. CI: confidence interval.

Table 3. Multivariable analyses of association of RA treatment variables with visits to a physician for sinus problem in the last 6 months.

Variable	OR (95% CI)	p
Age, yrs	0.99 (0.98, 0.99)	< 0.001
Sex (male = 1)	0.87 (0.74, 1.01)	0.068
Non-Hispanic White	1.30 (1.03, 1.64)	0.027
Education, yrs	1.02 (0.99, 1.05)	0.117
MTX	1.06 (0.93, 1.20)	0.371
Prednisone	0.98 (0.86, 1.11)	0.776
Infliximab	1.00 (0.88, 1.15)	0.973
Hydroxychloroquine	1.08 (0.93, 1.25)	0.313
Leflunomide	0.84 (0.70, 0.99)	0.041
Etanercept	1.21 (1.02, 1.42)	0.025
Adalimumab	1.09 (0.79, 1.51)	0.600
Sulfasalazine	0.68 (0.51, 0.90)	0.007
Fatigue, 0–10	1.04 (1.01, 1.07)	0.005
Pain, 0–10	1.00 (0.97, 1.03)	0.857
HAQ, 0–3	0.95 (0.85, 1.06)	0.333
Allergy ever	2.06 (1.80, 2.36)	< 0.001
Asthma ever	1.24 (1.06, 1.45)	0.006
FM (survey criteria score = 1)	1.22 (1.01, 1.46)	0.038
Etanercept vs infliximab	1.20 (1.00, 1.45)	0.050
Etanercept vs adalimumab	1.11 (0.77, 1.59)	0.587

adjusted rate of chronic sinusitis to be 1.96%. The case definitions of all of these reports differ and one must, therefore, be cautious in making comparisons.

There is some evidence that sinusitis is increased in immunocompromised patients[4,20,21] and in inflammatory bowel disease[3]. However, there are no reports of studies of sinusitis in RA or OA. A single report links chronic unexplained fatigue to sinus symptoms[22], a finding with similarities to the association we noted between sinus problems and fatigue.

With reference to RA, upper respiratory and sinus infections are more common in patients treated with anti-TNF than in controls in clinical trials[5], with very slight increases in those treated with adalimumab and for sinusitis in those treated with infliximab (12% vs 6%)[5]. In clinical trials, upper respiratory infections and sinusitis were the most frequently reported infections in patients receiving etanercept or placebo, and the rate of upper respiratory tract infections was 17% in the placebo group and 22% in the group treated with etanercept. There were no increases in the rates of serious infections (requiring hospitalization)[23].

The proximate reason for our study was the apparent high rate of sinusitis observed in patients with RA in the clinic and the identification of a patients with RA who had repeated sinus infection after starting an anti-TNF treatment.

However, our data indicate that sinus problems are not increased in patients with RA, and after adjustment for age and sex are even slightly reduced compared with OA, although the difference, though statistically significant, is small (24.8% vs 22.1%). We found that in RA sulfasalazine, although used by few patients (5.8%), has a protective effect on sinus problems (OR 0.62; 95% CI: 0.47–0.82) (Table 2). This reduction might be related to its antibacterial effect[24,25]. We also found that leflunomide had a reduced association with sinus problems (OR 0.83; 95% CI: 0.77–0.99).

Patients receiving etanercept had an increased risk of sinus infections in age and sex adjusted analyses of Table 2 (OR 1.21; 95% CI: 1.04–1.41). The effect was decreased in multivariable analyses of Table 3 (OR 1.16; 95% CI: 0.99–1.36). However, compared with infliximab the increased risk remained (OR 1.23; 95% CI: 1.03–1.48). There were too few patients receiving adalimumab for meaningful comparisons.

As might be suspected, we found the strongest associations with sinus problems to be with allergies and asthma. We also found an increase in pain, fatigue, and HAQ among patients with sinus problems. This is not surprising as each additional chronic condition almost always adds to general distress.

In summary, sinus problems are not increased in RA compared with OA and FM. Slight protective effects on sinus problems are noted with sulfasalazine and leflunomide, and a slight increase in risk of sinus problems is noted with etanercept.

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