Rheumatoid Arthritis Increases Risk of Infection Requiring Hospitalization; Risk Higher in Patients on Corticosteroids

Smitten AL, Choi HK, Hochberg MC, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol 2008;35:387–93.

Study Overview

Objective. To determine whether patients with rheumatoid arthritis (RA) are at increased risk of hospitalized infection compared with those without RA and to determine if the risk varies by RA treatment.

Design. Retrospective cohort study using claims data (1999–2006) from PharMetrics, a managed care medical and pharmacy claims database of insured patients in 61 U.S. health plans, with a nested case-control analysis.

Setting and participants. 24,530 patients with RA and a random sample of 500,000 patients without RA were analyzed. The RA cohort included patients aged ≥ 18 years with ≥ 2 physician visits more than 2 months apart for RA (ICD-9-CM code, 714). Medications for RA were classified as traditional disease-modifying antirheumatic drugs (DMARDs; ie, including but not limited to methotrexate, hydrochloroquine, and azathioprine), biologic DMARDs (ie, infliximab, etanercept, adalimumab, anakinra), or oral corticosteroids (daily doses, ≤ 5 mg, 6–10 mg, and ≥ 10 mg). All patients with a hospitalized infection in the RA cohort were included in a nested case-control analysis, with 5 controls selected from a subset of RA cohort patients with the same entry period into the study and equal follow-up time.

Main outcome measures. The main outcome measure was hospitalized infections identified from inpatient and outpatient encounters, defined by specific ICD-9-CM codes and reported as Cox hazards models adjusted for age, sex, calendar year at cohort entry, number of comorbid conditions, and whether the patient was taking a non-RA prescription medication at cohort entry. A secondary outcome was serious infection, defined as a hospitalized infection or infection requiring outpatient parenteral antibiotics. Rate ratios (RRs) of hospitalized infection for biologic DMARDs, traditional DMARDs, and corticosteroids were analyzed using conditional logistic regression to account for the matched design. The analyses were adjusted according to age and sex and controlled for concurrent medication use, visits to a rheumatologist, orthopaedic procedures, and provision of nonsteroidal anti-inflammatory drugs.

Main results. A total of 1993 cases of a first hospitalized infection were identified in the RA cohort versus 11,977 cases in the non-RA cohort. The rate of first hospitalized infection was significantly higher in the RA cohort (adjusted hazard ratio, 2.03 [95% confidence interval {CI}, 1.93–2.13]). Pneumonia was the most common hospitalized infection. Based on the case-control analysis, current use of biologic DMARDs was associated with an increased risk of hospitalized infection (RR, 1.21 [95% CI, 1.02–1.43]). Traditional DMARD use, specifically with methotrexate and hydrochloroquine, was associated with decreased hospitalized infection rates. Oral corticosteroid use increased risk in a dose-dependent fashion (overall RR, 1.92 [95% CI, 1.67–2.21]; ≤ 5 mg/day: RR, 1.32 [95% CI, 1.06–1.63]; 6–10 mg/day: RR, 1.94 [95% CI, 1.53–2.46]); ≥ 10 mg/day: RR, 2.98 [95% CI, 2.41– 3.69]).

Conclusion. Patients with RA are at increased risk of hospitalized infection compared with patients without RA. Use of oral corticosteroids in patients with RA is associated with a high and dose-dependent risk for infection requiring hospitalization. Use of biologic DMARDs is associated with a significant but smaller elevated risk for hospitalized infection in these patients compared with corticosteroid use.

Commentary

A widely held notion exists that patients with RA are at increased risk of infection, due to both the underlying disease complications (eg, chronic lung disease, immobilization, T-cell defects) as well as the side effects of chronic immunosuppressive medications. Until recently, large studies confirming this assumption were either absent or contradictory. Doran et al [1] found a significant increased risk of infection in patients with RA, a finding not confirmed in prior studies [2,3]. Whether biologic DMARD therapy increases serious infections is unclear. Many case reports have discussed this possible association, but Gonzalez et al [4] found no difference in mortality in patients with RA before and after the introduction of biologic DMARD therapy.

The study by Smitten et al convincingly demonstrates that patients with RA have an elevated risk for hospitalized infections and that DMARD therapy is associated with this risk. Interestingly, the risk of hospitalized infection was higher with corticosteroids in a clear dose-response fashion, whereas the risk for hospitalized infection among RA patients taking nonbiologic DMARDs was the same or less than in the control group.

This study had a number of strengths. It included a large number of patients in the RA group, 24% of whom were on biologic DMARDs. The population sample was a large nationally representative group of individuals from a well-established and well-linked claims database. The large sample size and detailed covariate data acquisition enabled the researchers to build models that well-adjusted for confounding variables, including comorbidities and other medications.

However, the study had several limitations. Given that a claims database was used, limited data were available on the patients' history of infections prior to hospitalization, immune status, and clinical measures of RA progression. Disease severity was therefore a potential confounding factor. Patients with RA on high doses of corticosteroids or those who have failed traditional DMARDs and require biologic DMARDs may have more aggressive disease. Whether patients with more aggressive disease are comparable to patients with more limited forms of RA requiring minimal therapy is debatable. Misclassification of these patients with limited RA (based on ICD-9-CM codes) was possible as well. Finally, Bristol-Myers Squibb provided data (but not funding) for the study and an employee of the company is included on the author list. This company makes abatacept, a new biologic DMARD, but this drug was not included in the analysis.

What can be discerned from these intriguing findings? First, patients with RA are at high risk for serious infection due to a combination of their underlying disease and medication use. As such, clinicians should be vigilant about monitoring these patients for infections and intervening early when infections arise. Second, biologic DMARDs do carry an elevated risk of infection, but corticosteroids carry a higher risk directly correlated to dose. Even low doses (≤ 5 mg/day) carried a statistically significant elevation in risk, which was greater than the risk conferred by biologic DMARDs. The editorial accompanying this study stated that because biologic DMARDs are probably more efficacious with fewer side effects, clinicians should consider switching to them and decreasing or stopping the use of routine corticosteroids in RA when possible [5].

Applications for Clinical Practice

Patients with RA are at high risk for hospitalized infection. Although much attention has been appropriately focused on the association of biologic DMARDs with serious infection (especially tuberculosis), clinicians should be aware of the significant risks posed by chronic corticosteroid therapy in RA and strive to titrate these patients to the lowest possible dose.

—Review by Asaf Bitton, MD

References

1. Doran MF, Crowson CS, Pond GR, et al. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population based study. Arthritis Rheum 2002;46:2287–93.
2. van Albada-Kuipers GA, Linthorst J, Peeters EA, et al. Frequency of infection among patients with rheumatoid arthritis versus patients with osteoarthritis or soft tissue rheumatism. Arthritis Rheum 1988;31:667–71.
3. Vandenbroucke JP, Kaaks R, Valkenburg HA, et al. Frequency of infections among rheumatoid arthritis patients before and after disease onset. Arthritis Rheum 1987;30:810–3.
4. Gonzalez A, Maradit Kremers H, Crowson CS, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum 2007;56:3583–7.
5. Coblyn JS. Infections, drugs, and rheumatoid arthritis. What have we learned [editorial]? J Rheumatol 2008;35:375–6.