Hematologic Malignant Neoplasms After Drug Exposure in Rheumatoid Arthritis

Sasha Bernatsky, MD, PhD; Ann E. Clarke, MD, MPH; Samy Suissa, PhD

Background: Rheumatoid arthritis is a severe inflammatory polyarthritis that requires long-term treatment with disease-modifying antirheumatic drugs. There is increasing concern about the influence of rheumatoid arthritis therapy on the risk for hematologic malignant neoplasms.

Methods: We used a case-control design nested in a cohort of 23,810 patients with rheumatoid arthritis assembled from administrative databases covering the population of Quebec, Canada. The study was carried out from January 1, 1980, through December 31, 2003. Case patients having hematologic malignant neoplasms were ascertained from physician billing and hospitalization records; each case patient was matched for age and sex with 10 control subjects. Adjusting for clinical variables and concomitant medications, we used conditional logistic regression to analyze potential associations between disease-modifying antirheumatic drug exposures and risk for hematologic malignant neoplasms. We estimated rate ratios attributable to each disease-modifying antirheumatic drug exposure.

Results: During the study, hematologic malignant neoplasms developed in 619 patients, including lymphomas in 346 patients, leukemia in 178 patients, and multiple myelomas in 95 patients. The unadjusted rate ratios for hematologic malignant neoplasms after drug exposures were as follows: methotrexate, 1.18 (95% confidence interval [CI], 0.99-1.40); azathioprine, 1.44 (95% CI, 1.01-2.03); and cyclophosphamide, 2.21 (95% CI, 1.52-3.20). Because biologic agents first appeared in the Régie d’Assurance Maladie du Quebec formulary in 2002, there were few exposures to these drugs. Adjusted estimates suggested that hematologic cancer risk was most elevated after exposure to cyclophosphamide (rate ratio, 1.84; 95% CI, 1.24-2.73). For lymphomas only, the adjusted rate ratio after cyclophosphamide exposure was 2.12 (95% CI, 1.33-3.54).

Conclusions: In this large cohort of patients with rheumatoid arthritis, the greatest relative risk for hematologic malignant neoplasms was noted after use of cyclophosphamide. Assessments of risk related to newer and emerging therapies should carefully consider previous and concomitant medication exposures.

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We identified a cohort of 23,733 patients with RA with DMARD exposures and no recorded history of cancer. At cohort entry, mean (SD) age was 61.7 (14.6) years. Most subjects (70.1%) were women, as expected in RA. The most common current DMARD exposures at cohort entry were methotrexate, antimalarial agents, and sulfasalazine. Subjects were followed up on average for a mean (SD) of 6.7 (5.1) years. This yielded a total of 158,067 person-years of follow-up, during which 619 hematologic malignant neoplasms developed, for an incidence rate of 391.6 cases per 100,000 person-years.

The demographics for the 619 case patients vs their 6,190 matched control subjects were as follows: mean (SD) age, 70.0 (12.4) years vs 70.2 (11.4) years; female sex, 63.4% for both cohorts; and mean (SD) number of physician visits during follow-up, 26.3 (26.1) vs 18.1 (14.2). The events occurred at a mean (SD) of 5.2 (3.9) years after cohort entry. There was a trend for a higher number of physician visits (calculated up to the index date only) for the cases compared with the controls, but variance was high. The prevalence of many extra-articular RA features (eg, vasculitis and scleritis) seemed similar among cases and controls, although the prevalence of Felty syndrome was more common among cases compared with controls (difference of 8.9%; 95% CI, 6.8-11.5). Neuritis and also slightly more common among cases (difference of 1.7%; 95% CI, 0.8-3.1).

At univariate analyses of the risk for hematologic malignant neoplasms, there was a statistically significant association only with azathioprine (RR, 1.44; 95% CI, 1.01-2.03) and cyclophosphamide (RR, 2.21; 95% CI, 1.52-3.20) therapies. The adjusted RR estimates reflecting the specific effect of each exposure, independent of whether the subjects were concomitantly receiving other medications, are given in the Table. As indicated by these estimates, the risk seemed to be most elevated with exposures to cyclophosphamide (RR, 1.84; 95% CI, 1.24-2.73). For anti-TNF agents, the confidence intervals were relatively wide, although the RR point estimate was elevated, in both univariate and adjusted estimates.

The most frequently noted specific types of hematologic malignant neoplasms were lymphoma (n=346), leukemia (n=178 cases), and multiple myeloma (n=95). For lymphoma only, the adjusted RR after methotrexate exposure was 1.23 (95% CI, 0.97-1.57); after azathioprine exposure, 1.09 (95% CI, 0.67-1.77); after cyclophosphamide exposure, 2.12 (95% CI, 1.33-3.54); and after anti-TNF exposure, 3.14 (0.58-17.1). Sensitivity analyses using cumulative exposures and 5-year intervals between exposures did not change the RR estimates appreciably.
There have been a handful of controlled studies evaluating DMARD use and risk for malignant neoplasm. Asten et al\textsuperscript{10} assessed cumulative exposures to these in a large (N=17 773) multicenter cohort of patients with rheumatic disease and found an increased risk for hematologic malignant neoplasms; however, disease severity was not controlled for. Two early case-control studies of the risk of hematologic malignant neoplasms in RA\textsuperscript{11,12} suggested a link with azathioprine and cyclophosphamide therapies, although not definitively. More recently, Baeklund et al\textsuperscript{13} showed an association when controlled for disease activity of hematologic malignant neoplasms with azathioprine use in RA.

Wolfe and Michaud,\textsuperscript{2} in their large clinic-based RA sample, estimated an approximate 3-fold increased risk for lymphoma in patients after anti-TNF exposure and no definite effects for methotrexate, compared with those not receiving either agent. In that study, there were insufficient data to completely explore disease severity. Geborek et al\textsuperscript{14} compared cancer risk in 1557 patients with RA treated with DMARDs, making some adjustment for disease severity. They reported no increased risk of cancer in RA overall, although they did note increased risk for lymphoma in those receiving anti-TNF agents compared with those receiving traditional DMARDs. After adjustment for baseline disease severity, the risk for lymphoma developing in the anti-TNF–treated patients was 5 times the risk in unexposed patients, though with a wide CI, making definitive conclusions impossible.

For a rare disease such as RA and a relatively infrequent outcome, studies using administrative databases can be efficient. However, this approach does not allow confirmation of the RA diagnosis or the outcome. Insofar as the RA diagnosis, combining billing codes with DMARD prescription data enhances the validity of the RA diagnosis, as has been demonstrated by other investigators.\textsuperscript{15,16} Some reassurance is provided in that the demographics for our cohort (ie, age and sex) were similar to those in clinical RA populations. For cancers identified through administrative data, though we cannot confirm these per se, we emphasize that discharge diagnoses in Canadian hospitalization databases are assigned by trained medical coders; validation work has shown that the discharge databases can be nearly as reliable as medical records.\textsuperscript{17} Hospital discharge diagnoses are the basis for the provincial tumor registry in Quebec. Similarly, as for physician billing data, some validation work has suggested that billing records in Quebec are valid and more accurate than patient self-reports.\textsuperscript{18} For these reasons, we believe our approach to the identification of malignant neoplasms is reasonable. However, as in all observational studies, caution must be used in interpretation of the results.

In pharmacoepidemiology, bias may arise if medication use occurs differentially according to preexisting risk for the outcome (channeling). We attempted to control for this using appropriate strategies. We purposely created a homogenous population with respect to the likelihood of drug exposure. This was done by assembling an RA cohort whose members all were exposed to DMARDs and by examining risk for DMARD type. In addition, we excluded subjects with a history of cancer. We also adjusted for correlates of RA disease severity, including glucocorticoid use, number of physician visits, and extra-articular RA features. Using glucocorticoid exposure as a surrogate of RA disease severity is not without problems. Initiation of steroid treatment may correlate with disease severity, but prolonged treatment could lead to better-controlled disease activity than in patients not treated with steroids.

Our adjusted analyses reflect the specific independent effects of each DMARD, adjusted for other DMARD exposures. Our cohort consisted of both prevalent and incident RA cases; thus, some medication exposures, if occurring before 1980, may not have been recorded. However, we do not consider this a major limitation of our study because widespread DMARD use began primarily in the 1980s.

For severe refractory RA, oral cyclophosphamide was a treatment option even up to the last decade.\textsuperscript{19} In

### Table. Crude and Adjusted RRs for Hematologic Malignant Neoplasms Related to DMARD Exposures\textsuperscript{a}

<table>
<thead>
<tr>
<th>DMARD</th>
<th>Case Patients (n=619)</th>
<th>Control Subjects (n=6190)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>308 (49.8)</td>
<td>2847 (46)</td>
<td>1.18 (0.99-1.40)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>40 (6.5)</td>
<td>285 (4.6)</td>
<td>1.44 (1.01-2.03)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>36 (5.8)</td>
<td>167 (2.7)</td>
<td>2.21 (1.52-3.20)</td>
</tr>
<tr>
<td>Anti-malarial agents\textsuperscript{c}</td>
<td>280 (45.2)</td>
<td>2699 (43.6)</td>
<td>1.08 (0.90-1.28)</td>
</tr>
<tr>
<td>Anti-TNF agents\textsuperscript{d}</td>
<td>3 (0.5)</td>
<td>12 (0.2)</td>
<td>2.46 (0.66-9.15)</td>
</tr>
<tr>
<td>All other DMARDs\textsuperscript{e}</td>
<td>222 (35.9)</td>
<td>2358 (38.1)</td>
<td>0.79 (0.73-1.07)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DMARD, disease-modifying antirheumatic drug; RR, rate ratio; TNF, tumor necrosis factor.

\textsuperscript{a}Exposures at any time between cohort entry and index date.

\textsuperscript{b}Case and control subjects were matched for age and sex in both crude and adjusted estimates. Adjusted estimates consider all concomitant drug exposures (including DMARD polytherapy, glucocorticosteroids, nonsteroidal anti-inflammatory drugs, and cyclooxygenase 2 inhibitors), number of physician visits up to index date, and extra-articular disease (eg, lung, hematologic, dermatologic, and neurologic).

\textsuperscript{c}Antimalarial agents include hydroxychloroquine sulfate and chloroquine.

\textsuperscript{d}Anti-TNF agents (infliximab and etanercept) were first listed in the Quebec provincial formulary in 2002.

\textsuperscript{e}Includes sulfasalazine, leflunomide, cyclosporine, gold compounds, minocycline, and penicillamine.
our cohort, the patients exposed to cyclophosphamide, compared with those not exposed to cyclophosphamide, demonstrated a greater prevalence of Felty syndrome (19.4% vs 6.4%; difference of 12.7% [95% CI for difference, 7.6-18.9]) and vasculitis (14.6% vs 0.4%; difference of 14.2% [95% CI for difference, 9.8-19.9]). Other types of extra-articular RA were similar between patients exposed to cyclophosphamide compared with those not exposed.

Because lymphoma is a cancer arising from lymphocytes, it is not surprising that diseases characterized by immune system dysregulation (including RA, among others) are associated with malignant transformation of lymphocytes. Similarly, T-cell large granular lymphocyte leukemia is a disorder often associated with autoimmune disorders, especially RA, and particularly in patients with Felty syndrome. This malignancy of cytotoxic T cells is characterized by dysregulated apoptosis and may be antigen driven.90 Controversy continues, however, as to how much of the total risk of hematologic malignant neoplasms in RA is related to the disease process itself vs to immunosuppressive medications; recent data suggest both aspects are likely important.13 Immunosuppressive drugs have been linked to the development of both leukemia and lymphomas, and immunodeficiency, whether innate or acquired, is a strong risk factor for certain lymphomas. In many cases, this association relates to the emergence of Epstein-Barr virus–driven malignant proliferations; however, in RA, this does not seem to be the only driving force.13 Impaired immune surveillance can prevent the deletion of abnormal cells, a phenomenon that may have been magnified in our study design, which focused on an older cohort.

In conclusion, in our large RA cohort, increased risk for hematologic malignant neoplasms was most evident with cyclophosphamide exposure. This emphasizes the need, when evaluating malignancy risk related to novel agents, for careful consideration of previous and concomitant medication exposures.

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REFERENCES


