

# Malignancies in Juvenile Idiopathic Arthritis: A Preliminary Report

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**ABSTRACT. Objective.** To present preliminary data on incidence of malignancy in juvenile idiopathic arthritis (JIA), compared to general population rates.

**Methods.** We examined cancer occurrence within JIA registries at 3 Canadian pediatric rheumatology centers. The subjects in the clinic registries were linked to regional tumor registries to determine the occurrence of invasive cancers over the observation period (spanning 1974–2006). The total number of cancers expected was determined by multiplying the person-years in the cohort by age, sex, and calendar year-specific cancer rates. The standardized incidence ratio (SIR, ratio of cancers observed to expected) was generated, with 95% confidence intervals.

**Results.** The study sample consisted of 1834 patients. The female proportion was 67.6%; average age at entry to cohort was 8.6 years (SD 5.1). The majority were Caucasian. Subjects contributed 22,341 patient-years (average 12.2, SD 7.8). Within this observation period, one invasive cancer occurred, compared to 7.9 expected (SIR 0.12, 95% CI 0.0, 0.70). This was a hematological cancer (Hodgkin's lymphoma), representing a SIR for hematological malignancies of 0.76 (95% CI 0.02, 4.21).

**Conclusion.** Only one invasive cancer was identified in this large sample of individuals with JIA, observed for an average of 12.2 years each. These data suggest that, at least in the initial years following diagnosis of JIA, the risk of invasive cancers overall is not markedly increased. The results do not rule out the possibility of a baseline increased risk of hematological malignancies. (First Release Jan 15 2011; J Rheumatol 2011;38:760–3; doi:10.3899/jrheum.100711)

## Key Indexing Terms:

MALIGNANCIES JUVENILE IDIOPATHIC ARTHRITIS CANCER INCIDENCE

In the past decade, much has been learned about cancer risk for adults with rheumatic diseases, including rheumatoid arthritis (RA). There are few data about malignancy in juvenile idiopathic arthritis (JIA). Recent surveillance data from the US Food and Drug Administration (FDA) have raised

concern about increased cancer risk related to anti-tumor necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) agents in pediatric populations<sup>1</sup>. However, because of the paucity of information regarding baseline cancer risk in JIA, it is unclear whether cancer risk after anti-TNF- $\alpha$  treatment is truly related to the drugs or if it is related to underlying risk conferred by JIA itself. To investigate baseline cancer risk in JIA, we assessed the incidence of observed malignancy in a large group of subjects with JIA, compared to general population cancer rates. Preliminary results are presented.

## MATERIALS AND METHODS

We examined cancer occurrence within the JIA clinic registries maintained at 3 Canadian pediatric rheumatology centers: Royal University Hospital, Saskatoon, Saskatchewan; Health Sciences Centre, Winnipeg, Manitoba; and Montreal Children's Hospital, Montreal, Quebec. The centers in Saskatoon and Winnipeg provide care for the entire provinces of Saskatchewan (population 1 million) and Manitoba (population 1.1 million), while the Montreal center provides care for the entire McGill University Health Network (over 60% of the area of Quebec, about 1.7 million residents). Patients with clinically confirmed JIA were entered into each cohort, the first date seen in clinic representing their cohort entry date. In each province, healthcare is universally accessible without charge.

The subjects in the clinic registries were linked to provincial tumor registries (covering the same population as each cohort) to determine the occurrence of invasive cancers over the observational period, which spanned the calendar years 1974–2006. A priori, we excluded in-situ can-

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cers, as these are not included in provincial general population cancer rates. Person-years of followup for each subject were calculated from the cohort entry date, and the first of 3 possible events: death, cancer, or the end of the study period. Pooling the data, we determined the total number of observed cancers occurring over the total person-years of observation. The total number of cancers expected to occur over the observation period was determined by multiplying the person-years in the cohort by the geographically matched age, sex, and calendar year-specific cancer rates, and summing overall person-years. The standardized incidence ratio (SIR; ratio of cancers observed to expected) was generated, along with 95% confidence intervals (CI), based on the assumption of cancer occurrence as a Poisson-distributed variable.

## RESULTS

The study sample consisted of 1834 patients: 369 from the Royal University Hospital (Saskatoon), 799 from the Health Sciences Centre (Winnipeg), and 666 from the Montreal Children's Hospital. The female proportion was 67.6%. The average age at entry to cohort was 8.6 years (standard deviation 5.1). The majority of cohort members were Caucasian. The JIA subtypes included oligoarticular (46%), polyarticular rheumatoid factor (RF)-negative (21%), polyarticular JIA RF-positive (7%), systemic (7%), psoriatic (7%), and enthesitis-related (12%). Subjects were observed for a total of 22,341 patient-years, with an average followup of 12.2 years (SD 7.8). Within this observation period, one invasive cancer occurred, compared to 7.9 expected (SIR 0.12, 95% CI 0.0, 0.70). This was a hematological malignancy (Hodgkin's lymphoma) that occurred in a case of enthesitis-related JIA (disease duration 2.4 yrs). This individual had not been exposed to disease-modifying agents. Over the observation period, the expected number of hematological malignancies is 1.3 (SIR 0.76, 95% CI 0.02, 4.21).

## DISCUSSION

Our preliminary data suggest that, at least in the initial years following diagnosis of JIA, the risk of invasive cancers overall may not be markedly increased. In the previously largest published cohort study ( $N = 896$ )<sup>2</sup> related to cancer in patients with juvenile chronic arthritis, 4 cancers occurred (types of cancers were not given), with an expected number of 4.24 cancers, and SIR of 0.94 (95% CI 0.26, 2.42). The data of Thomas, *et al*<sup>2</sup> preceded the use of anti-tumor necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) agents, and in our cohort very few patients (2%) were exposed to these drugs. Limiting the observation period in our study to patients not exposed to anti-TNF- $\alpha$  drugs, and pooling our results with those of Thomas, *et al*<sup>2</sup> and the 387 anti-TNF- $\alpha$ -naive person-years from one other observational cohort<sup>3</sup>, the baseline cancer incidence for JIA patients (not under biologic therapy) would be calculated as 0.2 events per 1000 patient-years. The expected number of cancer cases pooling over the 28,928 patient-years of these patients is 12.4, and the pooled SIR for JIA patients unexposed to biologics would be 0.38 (95% CI 0.10, 0.98).

The literature in addition reveals 7 studies on cancer

experience after anti-TNF exposure, published over the period 2000–2009 (Table 1)<sup>2,3,4,5,6,7,8,9,10</sup>. These studies altogether yield 3037 person-years from anti-TNF- $\alpha$ -exposed patients, over which time 4 cancers occurred (1.3 events per 1000 patient-years), with 1.08 cancers expected, for a SIR of 3.70 (95% CI 1.01, 9.47). These included a germ-cell tumor, 2 thyroid carcinomas, and a non-Hodgkin's lymphoma; all 4 of these occurred in JIA patients treated with etanercept (representing the most common biologic exposures in JIA), and at least 3 were receiving concomitant methotrexate treatment<sup>7,8</sup>. Age at cancer onset was provided only by Horneff, *et al* for 2 cancers (patients aged 17 and 16.5 years, very shortly after the etanercept was initiated)<sup>7</sup>. Horneff, *et al* do refer to one additional cancer (not included in their analyses), a non-Hodgkin's lymphoma that occurred some time after the initiation of anti-TNF- $\alpha$  agents<sup>7</sup>. Otherwise, in the study by Horneff, *et al*<sup>7</sup>, the cancers were detected within a relatively short time (several months to only a few weeks) after the initiation of etanercept, which perhaps suggests the clinical manifestation of a preexisting subclinical cancer.

Disease activity is itself potentially related to cancer risk, at least in adult RA<sup>11</sup>. Concomitant drugs also may be important, since the majority of anti-TNF- $\alpha$ -exposed patients with JIA developing cancer have been exposed previously and/or concomitantly to other disease-modifying agents<sup>11</sup>, most often methotrexate. However, the nested case-control study by Baecklund, *et al*<sup>11</sup> comparing 378 cases of lymphoma developing in adult RA patients with 378 matched RA controls was unable to demonstrate an increased risk of lymphoma related to methotrexate or other traditional disease-modifying agents. On the other hand, it is possible that although low-dose methotrexate alone may not be oncogenic, in combination with other immunomodulatory drugs it might have a synergistic effect in promoting cancer. The recent report in adults with RA by Askling, *et al*<sup>12</sup> suggested no overall elevation of cancer risk after anti-TNF- $\alpha$  exposures, although patients exposed to adalimumab were at an increased risk during the first year of exposure. The authors note that the effect of an anti-TNF drug within the first year of therapy may again simply reflect clinical manifestation of a preexisting subclinical cancer.

The FDA has described 48 reports of cancer arising in children who had been treated with anti-TNF- $\alpha$  agents (31 infliximab, 15 etanercept, 2 adalimumab), although the number of patient-years of exposure for patients with JIA was not known<sup>1</sup>. According to FDA reports, in children exposed to anti-TNF- $\alpha$  agents for all indications, lymphoma is the most common cancer (comprising half those reported); however, many of these lymphomas arise in cases of inflammatory bowel disease, not JIA. Also, in 88% of cases, there was some use of other immunosuppressants. The analyses suggested higher cancer rates (overall, and for lymphoma with infliximab, and only for lymphoma for etaner-

Table 1. Published cohort study data in juvenile arthritis.

| Study                   | Country           | Drugs                                    | Study Design                     | N    | Person-yr (mean) | Female, % | Mean Age <sup>†</sup> | Cancers <sup>††</sup><br>Obs | Exp  |
|-------------------------|-------------------|--|----------------------------------|------|------------------|-----------|-----------------------|------------------------------|------|
| Lovell <sup>4</sup>     | USA, 2008         | Etanercept*                              | Longterm followup of RCT         | 42   | 318 (7.6)        | 67        | 10.4                  | 0                            | 0.12 |
| Giannini <sup>3</sup>   | USA, 2009         | Etanercept +/- methotrexate <sup>#</sup> | Open-label study                 | 397  | 859 (2.2)        | 74.9      | 10.3                  | 0                            | 0.30 |
| Burmester <sup>5</sup>  | Germany, 2009     | Adalimumab                               | RCT/open-label                   | 171  | 398 (2.3)        | 78.9      | 11.8                  | 0                            | 0.14 |
| Prince <sup>6</sup>     | Netherlands, 2008 | Etanercept*                              | National TNF antagonist registry | 146  | 436 (3.0)        | 70        | 11.2                  | 0                            | 0.15 |
| Horneff <sup>7</sup>    | Germany, 2009     | Etanercept*                              | National TNF antagonist registry | 604  | 604 (1.0)        | 67        | 12.8                  | 3                            | 0.21 |
| Gerloni <sup>8</sup>    | Italy, 2008       | Infliximab/etanercept*                   | Clinical cohort                  | 163  | 398 (2.4)        | 76        | 17.1                  | 1                            | 0.15 |
| Lahdenne <sup>9</sup>   | Finland, 2003     | Infliximab/etanercept**                  | Clinical cohort                  | 24   | 24 (1.0)         | —         | 10.2                  | 0                            | 0.01 |
| Thomas <sup>2</sup>     | UK, 2000          | +/- DMARD***                             | Hospital database cohort         | 896  | 6,587 (7.4)      | 61        | 12.6                  | 4                            | 4.24 |
| Bernatsky <sup>10</sup> | Canada, 2009      | +/- DMARD***                             | Clinical cohort                  | 1834 | 22,341 (12.2)    | 67.6      | 8.6                   | 1                            | 7.9  |

<sup>†</sup> At start of observation period. <sup>††</sup> Cancers ascertained from clinical data, with Thomas, *et al* and Bernatsky, *et al* including cancer registry linkages. For Lovell, Gerloni, and Lahdenne, the expected number was not provided in the original report, but was estimated using sex and age-specific general population cancer rates. <sup>#</sup> 859 patient-years of observation occurred on etanercept +/- methotrexate; the study also produced 387 patient-years of methotrexate-only data, with no cancers occurring, and 0.16 cancers expected. \* Essentially all had previous and/or concomitant DMARD (usually methotrexate). \*\* Some patients (unknown number) exposed to DMARD. \*\*\* About a quarter of these subjects were exposed to DMARD. RCT: randomized controlled trial; Obs: observed; Exp: expected; TNF: tumor necrosis factor; DMARD: disease-modifying antirheumatic drug.

cept). The more pronounced risk related to infliximab may have been due to underlying disease type of the children exposed, or other medication exposures.

In our own data, the number of cancers observed overall was less than expected. We believe our methods were rigorous and were not likely to introduce bias; the cancer registries used are population-based and comprehensive. Theoretically it is possible that cancer events in patients with JIA are systematically less likely to be ascertained by cancer registries. However, we have previously shown that cancer registry linkage accurately detects cancers in rheumatic disease populations, at least in adults<sup>3</sup>. A decreased risk of cancer in JIA may of course be related to exposure to nonsteroidal antiinflammatory drugs (NSAID), since these agents have protective effects, not only for colorectal cancer but also breast and probably other cancer types<sup>8</sup>. However, these are only hypotheses. In adults with RA, in contrast to the well established increased risk of lymphoma, there are decreased risks related to colorectal and breast cancer<sup>9</sup>, and NSAID have been evoked as a potential explanation for this phenomenon as well.

In summary, our preliminary data suggest that, at least in the initial years following diagnosis of JIA, the risk of invasive cancers overall may not be increased. Even with the large number of patients, and 22,341 person-years of followup, we were unable to provide a very precise estimate for the SIR for hematological malignancies in JIA; the confidence interval was wide and included the possibility of increased risk. Our results are also potentially limited in the small number of specific minorities (e.g., blacks, Asians,

Hispanics, etc.) in our sample. There remains a need for further information on cancer risk in JIA, and its relationship to disease activity and drug exposures<sup>2</sup>. Several initiatives are under way (including our own multicenter collaboration of clinical pediatric cohorts from North America) that will soon provide better information for rheumatologists and patients and their families.

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