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Comparative cancer risk associated with methotrexate, other non-biologic and biologic disease-modifying anti-rheumatic drugs

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ABSTRACT

Objective: There is little information comparing the potential risk of cancer across conventional and biologic disease-modifying anti-rheumatic drugs (DMARDs) in patients with rheumatoid arthritis (RA). Methotrexate has not been the focus of most contemporary pharmacoepidemiologic studies of cancer.
Methods: We conducted a comparative effectiveness study with cancer as the outcome. A large observational cohort of RA was followed up from 2001 to 2010. Reports of any cancer prompted a confirmation process that included adjudication of the primary cancer records. We used a propensity score (PS) with relevant covariates and cohort trimming to improve the balance between DMARD cohorts. Cox proportional hazard regression models were constructed to estimate the risk of cancer with various DMARDs, all compared with methotrexate.
Results: We identified 6806 DMARD courses for analysis (1566 methotrexate; 904 nbDMARDs; 3761 TNF antagonists; 408 abatacept; and 167 rituximab). Non-biologic DMARDs (HR 0.17, 95% CI 0.05–0.65) and TNF antagonists (HR 0.29, 95% CI 0.05–0.65) were associated with a reduced adjusted risk of cancer compared with methotrexate. Abatacept (HR 1.55, 95% CI 0.40–5.97) and rituximab (HR 0.42, 95% CI 0.07–2.60) were similar in risk of cancer with methotrexate. These results were robust to sensitivity analyses. After controlling for DMARD exposures, risk factors for cancer included male gender, age, and alcohol consumption.
Conclusions: Cancer risk was elevated for methotrexate users compared with nbDMARDs and TNF antagonists.

Introduction

Patients with rheumatoid arthritis (RA) suffer from a higher risk of certain malignancies, such as non-Hodgkin's lymphoma [1,2]. This risk is likely related to the immune dysregulation associated with RA [3]. Methotrexate, the most common treatment for RA, has been linked to some cancers but is also used, in higher doses, as chemotherapy for other cancers [4,5]. This background of increased cancer risk related to RA itself, and methotrexate use provides a complex setting to assess relative cancer risk associated with other disease-modifying anti-rheumatic drugs (DMARDs).

Biologic DMARDs, such as tumor necrosis factor (TNF) antagonists, abatacept, tocilizumab, and rituximab, target specific aspects

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of the immune system and are efficacious in RA patients with an inadequate response to methotrexate [6–8]. Possible cancer risks for several of these agents have prompted regulators to mandate warnings [9]. Such warnings generate concerns for patients and providers as RA is a chronic disease, requiring long-term therapy. However, it is not clear how the potential cancer risk associated with these newer drugs compares with methotrexate.

Several studies support the possible risk of cancer associated with some of these agents, specifically TNF antagonists. A meta-analysis of randomized trials found that two monoclonal antibodies to TNF were associated with a 3.3-fold elevated cancer risk [10]. A meta-analysis of etanercept trials found an approximate doubling of the cancer risk [11]. Other meta-analyses of trials and observational studies have not found any substantial increase in overall cancer risk associated with TNF antagonists [12–14]. However, there have been concerns raised about skin cancer risk associated with TNF antagonists [15,16]. There are few studies, other than the relatively short-term randomized trials, regarding cancer risk of abatacept, tocilizumab, or rituximab in RA [17–19].

It is unlikely that randomized controlled trials will directly compare methotrexate with newer DMARDs in large-enough samples for long-enough periods to estimate comparative cancer risk. Observational drug studies have well-described and important limitations with respect to confounding bias [20]; however, this issue is more critical when examining a drug's potential benefits than risks. Unintended treatment effects, such as cancer, can be well studied in observational settings.

We undertook a study of the comparative risk of malignancy associated with DMARDs, comparing different agents with methotrexate, a treatment that most clinicians are comfortable using in routine practice and is a first-line therapy for most patients with RA. This study was carried out using the Consortium of Rheumatology Researchers of North America (CORRONA) registry.

Methods

Study cohort and data source

We examined data from the CORRONA registry covering the period 10/01/2001 to 11/30/2010. This cohort has been described in detail previously [21]. It is based in 132 rheumatology practices throughout the US. Subjects and rheumatologists complete questionnaires at study visits approximately every four months. Patients enter at different times in their treatment course, depending upon when they are first enrolled in the registry. Data are entered online via an electronic data capture system for the majority of sites, with centralized data entry by trained staff for the remaining sites. Incomplete sections of the forms are not accepted and returned to sites for completion as data queries.

Participants with RA were potentially eligible for the study cohort if they had at least two visits. We did not exclude subjects with a prior history of cancer, but subjects with reports of cancer who had evidence that the cancer was prevalent were excluded. In addition, all study activities have been reviewed and approved by a central Institutional Review Board. While CORRONA receives financial support from the manufacturers of several biologic DMARDs, they had no part in any aspect of these analyses. The first author (DHS) had possession of the primary data and vouches for the accuracy of the analyses.

Cancer end points

The adjudication process for cancer end points has been described and validated in prior work [22]. Briefly, all patient and/or rheumatologist reports of cancer after the baseline questionnaire are followed up with a confirmation form. This form asks the rheumatologist to verify that the initial questionnaire report was accurate. If this is the case, then medical records are sought to further adjudicate the presence of an incident cancer, including pathology, surgery, and oncology reports. These reports are then reviewed by two board-certified internal medicine specialists to determine the likelihood that the report represents a true incident cancer. All potential cases are categorized as "no cancer," "prevalent cancer," "possible cancer," "probable cancer," and "definite cancer."

Source documents were reviewed for each malignancy. Malignancies were defined as "definite" if a malignancy was reported on a biopsy report or from an oncologist or radiation oncologist. To be considered an incident malignancy, the date of diagnosis (month and year) also had to be submitted and had to have occurred after enrollment. For certain malignancies, note from an appropriate specialty was considered sufficient to designate the case as "definite" (e.g., skin cancer and dermatologist's note). If the documentation included the date of diagnosis and histology either in the note or handwritten on adverse event form, then the diagnosis was designated "probable." If either the histology or the date of diagnosis were not present, then the case was designated "possible." For the sake of these analyses, only cancers adjudicated as probable or definite cancers were included as end points.

DMARD Exposures

The exposures of interest for these analyses were both non-biologic—methotrexate separate from other nbDMARDs—and biologic DMARDs. Most patients use multiple DMARDs concurrently for RA. Since our primary interest was to assess the comparative safety of newer DMARDs compared with methotrexate, we created explicit categories of these agents, including TNF antagonists, abatacept, tocilizumab, and rituximab. (There were not adequate numbers of tocilizumab users during the study period, and so this category was dropped and patients were censored after starting the use of this agent.) There was no distinction made between biologic DMARD monotherapy and combination biologic with concomitant non-biologic DMARD use, thus some biologic users also used methotrexate.

Methotrexate was considered the reference exposure because it is the standard of care for RA therapy. Some patients used other non-biologic DMARDs (such as leflunomide, sulfasalazine, or hydroxychloroquine) and this defined a separate exposure category (non-biologic DMARD or nbDMARD). We excluded person-time when subjects used both methotrexate and other nbDMARDs. Since there were relatively few users of other nbDMARDs (e.g., cyclosporine, gold, minocycline, and D-penicillamine), they were excluded. In typical clinical care, patients start with non-biologic DMARDs and, if inadequate response, progress to TNF antagonists, and then to other biologic DMARDs. Thus, we allowed patients to contribute person-time to multiple exposure groups as different observations. If there was only one visit with a given drug exposure without information at a follow-up visit about this exposure, then the duration of use could not be determined and the exposure period was excluded.

Since our interest was the cancer risk associated with biologic DMARDs, our primary exposure definition considered a patient always exposed to a biologic DMARD once they had used their first dose of a biologic DMARD. However, we imposed a "hierarchy" to the biologic DMARDs that reflects the fact that most patients use a TNF antagonist before another biologic DMARD. Patients contributed person-time to the TNF antagonist group from the time they began such treatment until they switched to another biologic DMARD (abatacept or rituximab). A similar hierarchy was applied to the methotrexate and other nbDMARDs, allowing patients to contribute