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Risk of Cancer After Initiation of Targeted Therapies in Patients With Rheumatoid Arthritis and a Prior Cancer: Systematic Review With Meta-Analysis

Amélie Wetzman,¹ Cédric Lukas,¹ Cécile Gaujoux-Viala,² Ronac Mamtani,³ Thomas Barnetche,⁴ Bernard Combe,¹ Jacques Morel,¹ and Paulina Szafors¹

Objective. To determine the risk of recurrent or new malignancy with exposure to targeted disease-modifying antirheumatic drugs (DMARDs) in adults with rheumatoid arthritis (RA), axial spondyloarthritis (SpA), or psoriatic arthritis (PsA) and a history of cancer.

Methods. We performed a systematic search of the literature for articles published up to June 2019 that investigated adults with RA, axial SpA, or PsA who had a history of cancer and received biologic or targeted synthetic DMARDs (bDMARDs or tsDMARDs). We compared the risk of relapse or occurrence of new cancer between patients with and without bDMARDs. Rate ratios (RRs) with 95% confidence intervals (95% CIs) were estimated. The heterogeneity of the studies was evaluated by the Cochran Q test and the I^2 statistic.

Results. We included 24 observational studies of chronic inflammatory arthritis; of those, 12 were included in the meta-analysis of RA patients receiving bDMARDs. As compared with RA patients with a history of cancer and not receiving bDMARDs, for those receiving any bDMARD, the overall RR for risk of neoplasia was 1.09 (95% CI 0.92–1.32; $P = 0.31$, $I^2 = 8\%$); with tumor necrosis factor inhibitors, it was 1.11 (95% CI 0.85–1.46; $P = 0.45$, $I^2 = 48\%$), and with rituximab, it was 0.79 (95% CI 0.41–1.53; $P = 0.49$, $I^2 = 0\%$). The RR for risk of recurrence for skin cancer was 1.32 (95% CI 1.02–1.72; $P = 0.04$, $I^2 = 0\%$) and for breast neoplasia 1.21 (95% CI 0.84–1.72; $P = 0.31$, $I^2 = 0\%$).

Conclusion. Apart from skin cancers including melanoma, the risk of recurrent or new cancer is not increased with the initiation of bDMARDs for RA as compared with no bDMARDs.

INTRODUCTION

Biologic disease-modifying antirheumatic drugs (bDMARDs) have revolutionized the treatment of rheumatoid arthritis (RA) by achieving remission and improving quality of life (1). These treatments have then been used to treat other chronic inflammatory arthritis diseases such as axial spondyloarthritis (SpA) and psoriatic arthritis (PsA) (2,3). In recent years, a new therapeutic class has emerged: targeted synthetic DMARDs (tsDMARDs).

RA patients have shown an increased risk of cancer as compared with the general population, especially for lymphomas and lung cancer (4). Interfering with the immune system, bDMARDs,

in particular anti-tumor necrosis factor (TNF) agents, were initially suspected to increase the incidence of cancers (5,6). Safety data for bDMARDs showed no increased risk of cancer (solid and lymphoproliferative) in patients with RA without a history of cancer (7–10). For nonmelanoma skin cancers (NMSCs), the risk seemed increased with TNF inhibitors as compared with placebo or no DMARDs, thus requiring regular monitoring by a dermatologist for patients receiving anti-TNF agents (9). However, most randomized studies excluded patients with a history of cancer, which limits the use of bDMARDs in this population.

Some recommendations suggest waiting for 5-year oncologic remission before initiating treatment with bDMARDs or

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¹Amélie Wetzman, MBBS, Cédric Lukas, MD, PhD, Bernard Combe, MD, PhD, Jacques Morel, MD, PhD, Paulina Szafors, MD: University of Montpellier, Montpellier, France; ²Cécile Gaujoux-Viala, MD, PhD: University of Montpellier, Montpellier, and Nîmes University Hospital, Nîmes, France; ³Ronac Mamtani, MD: University of Pennsylvania, Philadelphia; ⁴Thomas Barnetche, PhD: Fédération Hospitalo-Universitaire and Centre Hospitalier Universitaire, Pellegrin, Bordeaux, France.

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Address correspondence via email to Paulina Szafors, MD, at p-szafors@chu-montpellier.fr.

SIGNIFICANCE & INNOVATIONS

- This is the first meta-analysis evaluating the risk of recurrent or new cancers in patients with chronic inflammatory arthritis and a history of neoplasia who were exposed to biologic or targeted synthetic disease-modifying antirheumatic drugs (hereafter bDMARDs because studies were only found for bDMARDs).
- Our study suggests that the risk of recurrent or new cancer is not increased for rheumatoid arthritis patients with a history of cancer (solid, hemopathy, cervical intraepithelial neoplasia, or nonmelanoma skin cancers) and initiating treatment with bDMARDs as compared with patients not receiving bDMARDs.
- For rheumatoid arthritis patients with prior cancer and receiving a tumor necrosis factor inhibitor or rituximab, the risk of recurrent or new cancer was not increased as compared with patients naive to biologic treatment.
- The risk of relapse or a new skin cancer was increased for rheumatoid arthritis patients with a history of malignancy, apart from skin cancers excluding melanoma.

tsDMARDs for patients with chronic inflammatory arthritis and a history of solid cancer (1,11). Rituximab is preferred with a history of lymphoma (1,11–14). The question of starting treatment with bDMARDs or tsDMARDs is frequent in patients with a history of neoplasia. In view of the current lack of evidence for patients with a history of cancer, delayed treatment with bDMARDs or tsDMARDs may lead to insufficient control of the rheumatic condition.

Two meta-analyses studied cancer recurrence or new cancers in inflammatory diseases (15,16) and found no increased risk for patients with RA or chronic inflammatory bowel disease (IBD) and a history of cancer who started treatment with a bDMARD. In these 2 meta-analyses performed in gastroenterology, only anti-TNF agents were evaluated because the population of interest was mainly patients with IBD. However, the therapeutic arsenal for patients with chronic inflammatory arthritis is extensive. The objective of this study was to determine the risk of recurrent or new cancer in patients with chronic inflammatory arthritis and a history of malignancy who received bDMARDs or tsDMARDs.

MATERIALS AND METHODS

Data sources and searches. We performed a systematic search of the databases Embase and the Cochrane library for articles published up to June 2019 and MEDLINE via PubMed for articles published up to March 2020 with no limitation on publication year or journal. We supplemented these results with a manual search in the bibliographies of the selected studies and the abstracts of the scientific congresses of the American College of

Rheumatology (ACR) and European Alliance of Associations for Rheumatology from 2016 to 2018.

The first part related to chronic inflammatory arthritis: RA, axial SpA, and PsA. The second part related to interventions by biologic treatment (TNF inhibitor, rituximab, abatacept, interleukin 6 inhibitor [IL-6; tocilizumab], IL-12 and IL-23 inhibitor [ustekinumab], IL-17 inhibitor [secukinumab and ixekizumab]) or tsDMARDs with JAK inhibitor (baricitinib, tofacitinib). The last part of the search included terms for a history of cancer. The meta-analysis followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (17) and the Cochrane collaboration guidelines (18).

Article selection. Two independent investigators (AW and PS) selected English-language articles on the basis of the titles and abstracts, then by reading the full text. In case of disagreement, consensus was reached with a third author (JM). Inclusion criteria were observational studies investigating the recurrence of cancer or new cancer in patients with RA, axial SpA, or PsA and a history of cancer and comparing patients receiving bDMARDs or tsDMARDs versus no DMARDs or placebo. Studies were excluded when their inclusion criteria did not mention or exclude patients with a history of cancer. We also excluded case reports, reviews, and randomized studies. An email was sent to the first author if the article was not available online.

Data selection. Two investigators (AW and PS) collected data by using a predefined form. The main objective was to analyze the number of new or recurrent cases of cancer in patients with chronic inflammatory arthritis who received DMARDs. The number of events was collected in each subgroup according to the rheumatic condition, biologic treatment used, and type of cancer (lymphoproliferative malignancies, solid cancer, skin cancer). The hazard ratios (HRs) and 95% confidence intervals (95% CIs) were collected, as were the characteristics of populations and cancers

). Ronac Mamtani allowed us to use data from his study (19) to calculate the number of patients in the meta-analysis.

Quality assessment. The quality assessment of the studies followed the Cochrane collaboration guidelines (20). A second assessment scale involved the Newcastle-Ottawa Scale (21)

Statistical analysis. To assess the risk of recurrence between RA patients who received DMARDs and controls, we used the rate ratio (RR). If RRs were not mentioned in the article,

they were calculated from the data extracted from the study. Rev-Man 5.3 was used to calculate the cumulative risks for each group, with their 95% CIs. Two-sided *P* value less than 0.05 was considered statistically significant. The heterogeneity of studies was evaluated with the Cochran Q test and the I^2 statistic. We performed subgroup analyses according to the treatment (TNF inhibitor or rituximab) and type of recurrent cancer (breast cancer, NMSCs, melanoma, or cervical cancer in women with a history of precancerous lesion of the uterus).

RESULTS

Literature search results and trial characteristics.

Our search strategy identified 1,657 articles (Figure 1): 653 from PubMed until March 2020, 931 from Embase, 71 in Cochrane until March 2019, and 2 from conferences. After reading the titles and abstracts, we selected 169 articles meeting the inclusion criteria, then 24 articles (19,22–44) after reading the full text, including 12 for the meta-analysis (19,25–28,33,36–39,41,43).

The meta-analysis involved observational cohorts of patients with RA. For patients with axial SpA or PsA, the retrieved cohort studies had too much missing data (number of patients with a history of cancer) or a small sample size (<10 patients). We did not retrieve any study of patients with a history of cancer and

receiving tsDMARDs. Characteristics of studies included in the meta-analysis are detailed in Table 1 and all studies retrieved from the systematic review in Table 2.

The 12 articles selected for the meta-analysis included 5 controlled cohorts (4 from Europe and 1 from the US). Studies were all multicentric and retrospective (studies of registries). Some investigated all types of cancer (27) and others all cancers without skin cancers (39,41), only solid cancers (19,43), melanoma and NMSCs (26,28,37,38), or cancers of the cervix in patients with a history of cervical dysplasia (25,33,36). When the same cohort was used for several studies, each study examined only 1 type of cancer and therefore excluded the other types (e.g., a history of cancer or recurrence).

For all RA cohorts included in the meta-analysis, most patients received anti-TNF drugs. Other patients received abatacept (33,38,41), rituximab (27,33,38,39,41), or tocilizumab (33,41), and some received anakinra (4 patients) or other biologics (6 patients) in 1 study (33). Patients receiving bDMARDs were compared to those who were biologics-naïve.

Patients were followed up between 1998 and 2015, from 3.9 to 6.8 years. Follow-up was variable across studies or not reported (26–28,33,37,38,41). Silva-Fernández et al (39) followed patients receiving anti-TNF alpha for a mean of 6.8 years, rituximab for a mean of 3.9 years, and no bDMARDs for a mean of

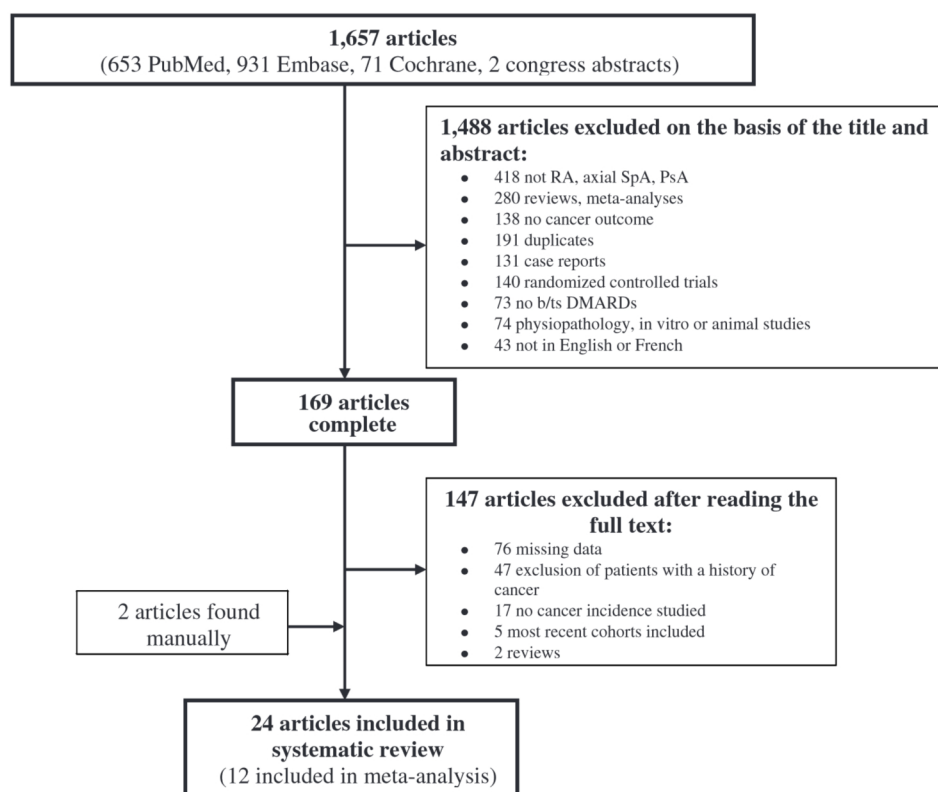


Figure 1. Flow chart of the selection of articles. b/ts = biologic/targeted synthetic; DMARDs = disease-modifying antirheumatic drugs; PsA = psoriatic arthritis; SpA = spondyloarthritis; RA = rheumatoid arthritis.

Table 1. Characteristics of studies included in the meta-analysis*

Author, year (ref)	Cohort, country	Initial cancer type	DMARD	Patients, no.	Follow-up, years	Events, no.	PY	Rate/1,000 PY	HR (95% CI) [adjustment]
Raaschou et al, 2018 (43)	ARTIS, Sweden	Solid	TNFi, no bDMARD	TNFi: 467, nb-D: 2,164	TNFi: 5.3, nb-D: 4.3	TNFi: 42, nb-D: 155	NR	TNFi: 17, nb-D: 16.5	1.06 (0.73–1.54) [†]
Dreyer et al, 2018 (41)	DANBIO, Denmark	All cancer cases, without NMSC	TNFi, ABA, RTX, TOC, no bDMARD	TNFi, ABA, RTX, TOC: 312, nb-D: 1,176	NR	TNFi, ABA, RTX, TOC: 27, nb-D: 70	TNFi, ABA, RTX, TOC: 953, nb-D: 2,461	NR	1.13 (0.71–1.80) [age, sex, calendar time, cancer site]
Scott et al, 2016 (38)	Medicare, US	NMISC	TNFi, MTX, ABA, MTX, RTX, MTX	NR	NR	TNFi: 109, MTX: 335, ABA: NR, MTX: 319, RTX: NR, MTX: 320	TNFi: 1.47, MTX: 4.63, ABA: 66, MTX: 4.31, RTX: 19, MTX: 4.30	NR	TNFi, MTX: 1.49 (1.03–2.16) [†], ABA, MTX: 1.40 (0.48–4.03) [†], RTX, MTX: 1.44 (0.26–8.08) [†]
Wadström et al, 2016 (36)	ARTIS, Sweden	CIN 1, 2, or 3 ^S	TNFi, no bDMARD	TNFi: 685, nb-D: 2,036	TNFi: 6.05, nb-D: 5.06	TNFi: 3, nb-D: 4	NR	TNFi: 0.072, nb-D: 0.039	Not computed due to low number of events
Mamtani et al, 2016 (19)	Medicare, US	Breast	TNFi, no bDMARD	TNFi: 273, nb-D: 892	NR	TNFi: 17, nb-D: 52	NR	NR	1.11 (0.64–1.95)
Silva-Fernández et al, 2016 (39)	BSRBR-RA, UK	All cancer cases, without NMSC	TNFi, no bDMARD, RTX, no bDMARD	TNFi: 243, nb-D: 159, RTX: 23, nb-D: 159	TNFi: 6.8, nb-D: 6.6, RTX: 3.9, nb-D: 6.6	TNFi: 53, nb-D: 46, RTX: 2, nb-D: 46	NR	TNFi: 33.3, nb-D: 53.8, RTX: 24.7, nb-D: 53.8	TNFi, nb-D: 0.56 (0.36–0.88) [age, sex, smoking status], RTX, nb-D: 0.44 (0.11–1.82) [age, sex, smoking status]
Raaschou et al, 2016 (37)	ARTIS, Sweden	Squamous cell [S], basal cell [B]	[S] TNFi, no bDMARD; [B] TNFi, no bDMARD	[S] TNFi: 74, nb-D: 466; [B] TNFi: 91, nb-D: 250	NR	[S] TNFi: 10, nb-D: 97; [B] TNFi: 17, nb-D: 41	[S] TNFi: 390, nb-D: 1,85; [B] TNFi: 269, nb-D: 602	[S] TNFi: 0.026, nb-D: 0.053; [B] TNFi: 0.063, nb-D: 0.068	[S] TNFi, nb-D: 0.99 (0.44–2.10); [B] TNFi, nb-D: 1.19 (0.67–2.15)
Cordtz et al, 2015 (33)	DANBIO, Denmark	CIN 1, 2, or 3 ^S	bDMARD, no bDMARD [†]	bDMARD: 23, nb-D: 442	NR	bDMARD: 0, nb-D: 0	NR	bDMARD: 0, nb-D: 0	Not computed due to low number of events
Strangfeld et al, 2013 (27)	RABBIT, Germany	Lymphomas [L], solid [S]	[L] TNFi, RTX, no bDMARD; [S] TNFi, RTX, no bDMARD	[L] TNFi, RTX: 40, nb-D: 30; [S] TNFi, RTX: 298, nb-D: 186	NR	[L] TNFi, RTX: 3, nb-D: 0; [S] TNFi, RTX: 28, nb-D: 13	NR	[L] TNFi: 45, RTX: 34, nb-D: 0; [S] TNFi: 57, RTX: 39, nb-D: 36	NR

(Continued)

Table 1. (Cont'd)

Author, year (ref.)	Cohort, country	Initial cancer type	DMARD	Patients, no.	Follow-up, years	Events, no.	PY	Rate/1,000 PY	HR (95% CI) [adjustment]
Raaschou et al, 2013 (28)	ARTIS, Sweden	Melanoma	TNFi, no bDMARD	TNFi: 54, nb-D: 295	NR	TNFi: 3, nb-D: 10	NR	NR	3.2 (0.8–13.1) [age, sex]
Mercer et al, 2012 (25)	BSRBR-RA, UK	CIN 3	TNFi, no bDMARD	TNFi: 190, nb-D: 48	TNFi: 5.2, nb-D: 3.9	TNFi: 0, nb-D: 2	TNFi: 893, nb-D: 159	TNFi: 0, nb-D: 13	NR
Mercer et al, 2012 (26)	BSRBR-RA, UK	NMSC	TNFi, no bDMARD	TNFi: 177, nb-D: 106	NR	NR	NR	TNFi: 46.2, nb-D: 79.8	0.7 (0.26–1.94) #

* 95% CI = 95% confidence interval; ABA = abatacept; bDMARD = biologic disease-modifying antirheumatic drug; CIN = cervical intraepithelial neoplasia; HR = hazard ratio; MTX = methotrexate; nb-D = no biologic DMARD; NMSC = nonmelanoma skin cancer; NR = not reported; PY = person-year; ref. = reference; RTX = rituximab; TNFi = tumor necrosis factor inhibitor; TOC = tocilizumab.

† Education level, comorbid conditions, sex, birth year (± 10 years), year of diagnosis (± 5 years) of the index cancer, cancer type, and index cancer stage.

‡ TNFi or RTX or ABA exposure prior to the incident NMSC diagnosis.

§ Including cervical cancer in situ and adenocarcinoma in situ.

¶ Biologic treatment for number of patients with RA in the Cordtz study: adalimumab 66; etanercept 53; infliximab 81, golimumab 7, and certolizumab 8; ABA 0; anakinra 4; RTX 5; TOC 3, and other 6.

Age, sex, smoking, previous exposure to ciclosporin and azathioprine, nonsteroidal antiinflammatory drugs, and differences in baseline characteristics.

Table 2. Characteristics of the studies included in the systematic review*

Author, year, country (ref.)	CIA	DMARD	Control	Initial cancer type	Patients, no.	Follow-up, years	Events, no.	PY	Rate/100 PY	HR (95% CI)
Winthrop et al, 2018, US/Puerto Rico (44)	RA	RTX	No	All cancers without NMSC	134	NR	7	NR	NR	NR
Yamasaki, 2018, Japan (40)	RA	bDMARD	No bDMARD	Solid	bDMARD: 15, no bDMARD: 15	NR	bDMARD: 40%, no bDMARD: 0.70%	NR	NR	NR
Atzeni et al, 2018, Italy (42)	axSpA	TNFI	No	NR	50	NR	10	NR	NR	11.2 (4.4–28.4)
Gottenberg et al, 2016, France (35)	RA	RTX, ABA	No	NR	RTX: 270, ABA: 55	RTX: 5.2, ABA: 4.6	RTX: 48, ABA: 5	RTX: 1,404, ABA: 253	NR	NR
Aaltonen et al, 2015, Finland (22)	RA	TNFI, RTX	No bDMARD	NR	bDMARD: 143, no bDMARD: 77	NR	4	NR	NR	NR
Berghen et al, 2015, Belgium (34)	RA	TNFI	No	All cancers without NMSC	9	NR	2	NR	NR	NR
Phillips et al, 2015, US (31)	RA	TNFI	No bDMARD	Head and neck†	TNFI: 31, no bDMARD: 149	NR	TNFI: 5, bDMARD: 44	NR	NR	0.75 (0.3–1.8)
Van Lümig et al, 2015, The Netherlands (32)	RA	TNFI	Psoriasis	NMSC	RA: 5, psoriasis: 6	NR	RA: 2, psoriasis: 2	NR	NR	NR
Cordtz et al, 2015, Denmark (33)	axSpA, PsA	bDMARD	No bDMARD	CIN 1, 2, or 3‡	bDMARD: 62, no bDMARD: 107	NR	bDMARD: 0, no bDMARD: 0	NR	0	Not computed due to low numbers
Sebastiani et al, 2014, Italy (24)	RA	RTX	No	NR	13	NR	0	NR	NR	NR
Bae et al, 2014, South Korea (29)	RA, axSpA	TNFI	No	NR	22	NR	0	NR	NR	NR
Westhovens et al, 2014, Belgium (30)	axSpA	TNFI	No	NR	3	NR	1	NR	NR	NR
Silmani et al, 2011, France (23)	RA	RTX	No	All cancers	26	23.1	1	4.3	NR	NR

* 95% CI = 95% confidence interval; ABA = abatacept; axSpA = axial spondyloarthritis; bDMARD = biologic disease-modifying antirheumatic drug; CIA = chronic inflammatory arthritis; CIN = cervical intraepithelial neoplasia; HR = hazard ratio; NMSC = nonmelanoma skin cancer; NR = not reported; PsA = psoriatic arthritis; PY = person-years; RA = rheumatoid arthritis; ref. = reference; RTX = rituximab; TNFI = tumor necrosis factor inhibitor.

† Recurrence and death.

‡ Including cervical cancer in situ and adenocarcinoma in situ.

6.6 years. Raaschou et al (43) followed patients receiving bDMARDs for a mean of 5.3 years and the control group for a mean of 4.3 years. In the majority of studies, a bDMARD was used for the first time (19,25,26,28,36,37,39,43). For the other cohorts, this information was not mentioned in the article. The time from remission of the first cancer to the introduction of bDMARDs varied among studies: at least 1 year for some (19,38), 6 months for Raaschou et al (43) (median of 7.9 years for bDMARDs, 7.6 years for no bDMARDs), or during the 5 years after oncologic remission (25,36).

Studies mostly had a moderate risk of bias. No study was excluded because of low quality assessment.

Systematic review: chronic inflammatory arthritis with a history of cancer and receiving bDMARDs. Four articles investigated the risk of cancer in patients with axial SpA treated with bDMARDs (29,30,33,42) (Table 2). Atzeni et al (42) found a history of neoplasia as a risk factor for new neoplasia or disease recurrence: in this Italian observational cohort, 10 of the 50 patients with a new cancer during follow-up had a history of cancer (80% solid cancer and the others nonmelanoma skin tumors), with HR 11.2 (95% CI 4.4–28.4; $P < 0.001$). Bae et al (29) retrospectively analyzed 22 patients with RA or axial SpA treated with a TNF inhibitor, without a control group. During a mean follow-up of 40 months, no new neoplasia was detected.

Finally, other US (44), Finnish (22), Belgian (34), Dutch (32), French (23,35), Italian (44), and Japanese (40) cohort studies followed RA patients receiving bDMARDs. They reported a few cases of cancer recurrence in patients with a history of neoplasia.

However, because of small numbers or lack of data, we were unable to calculate RRs and could not add them to our meta-analysis. Philips et al (31) found no increased risk of recurrence or mortality of head and neck cancer in RA patients receiving a TNF inhibitor versus no bDMARDs (HR 0.75 [95% CI 0.31–1.85]; $P = 0.54$).

Meta-analysis: RA patients with a history of cancer and receiving bDMARDs. Overall risk of new or recurrent cancer. Among the 26 studies, 9 cohort studies (19,26–28,37–39,41,43) were included to calculate the risk of recurrent or new cancers of all types (solid, lymphomas, and skin cancer, excluding invasive cervical cancer) in RA patients receiving bDMARDs (TNF inhibitor, rituximab, tocilizumab, abatacept) versus no bDMARDs. The RR was 1.09 (95% CI 0.92–1.29; $P = 0.31$) with little heterogeneity between studies ($I^2 = 8%$, $P = 0.37$) (Figure 2). The number of patients was at least 7,560: 1,930 receiving bDMARDs and 5,630 no bDMARDs. The exact number of patients could not be calculated, nor could the number of new cancers be calculated (38) because of unavailable data. Dreyer et al (41) also found no increased risk of cancer (all types, except NMSC) for patients starting bDMARDs <5 and >5 years after the first cancer diagnosis (HR 0.92 [95% CI 0.71–2.18] and 1.25 [95% CI 0.40–2.10], respectively) as compared with patients not receiving bDMARDs.

Risk of new or recurrent cancer with anti-TNF therapy. Eight studies (19,26–28,37–39,43) included patients treated with a TNF inhibitor, at least 1,494 patients, compared to 4,454 control patients (at least 164 new tumors occurred in patients receiving anti-TNF agents and 414 in patients not receiving bDMARDs; data missing for Mercer et al and Scott et al [26,38]). For these patients, the risk of cancer recurrence was not significantly

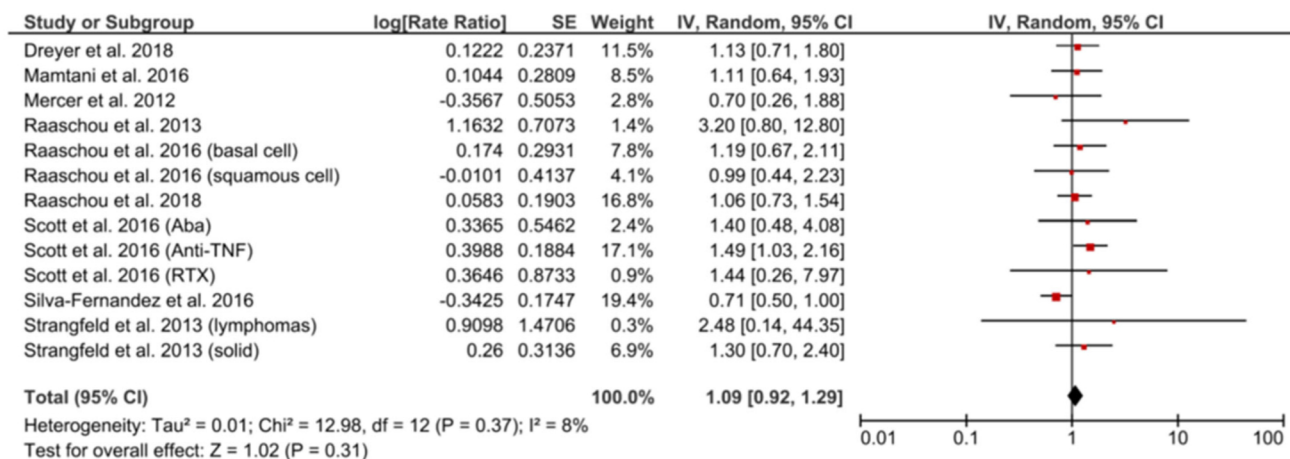


Figure 2. Risk of recurrence or new cancer in patients with rheumatoid arthritis with a history of cancer and receiving biologic disease-modifying antirheumatic drugs (bDMARDs) versus no bDMARDs. The size of the squares corresponds to the weight of each study. 95% CI = 95% confidence interval; Aba = abatacept; anti-TNF = anti-tumor necrosis factor; IV = inverse variance; RTX = rituximab.

increased (RR 1.11 [95% CI 0.85–1.46]; $I^2 = 48\%$, $P = 0.41$) (Figure 3A). For Raaschou et al (43), the time between cancer remission and initiation of bDMARDs was similar between the anti-TNF and no-bDMARDs groups. Silva-Fernández et al (39) did not specify the minimum duration for inclusion of patients, but patients initiating a TNF inhibitor had a longer duration of remission than patients not receiving bDMARDs (mean 11.5 and 7.9 years, respectively), and those receiving rituximab had a mean duration of remission shorter than the control group (5.4 years). Raaschou et al (43) showed no significant difference in risk among patients starting bDMARDs during the first 2 years after a cancer diagnosis (solid and hemopathy), between 2 and 5 years after or >5 years after ($P = 0.91$).

Risk of new or recurrent cancer with rituximab. Among the 26 studies analyzed, 3 provided the required data to calculate the risk of a new cancer in patients receiving rituximab (27,38,39). The number of patients with a second cancer or cancer recurrence was 11 of 124 receiving rituximab and 59 of 281 not receiving bDMARDs (data missing for Scott et al [38]). The risk of recurrent cancer was not significantly increased (RR 0.79 [95% CI 0.41–1.53]; $I^2 = 0\%$, $P = 0.65$) (Figure 3B).

Risk of new or recurrent cancer: breast cancer, invasive cervical cancer, or skin cancer. We found 2 studies (19,43) for patients with a history of breast cancer. The studies included 496 patients with a history of breast cancer who were exposed to anti-TNF agents: 44 experienced a recurrent or new breast tumor,

as did 2,002 patients in the control group, including 145 new cancers. The risk of new breast cancer or cancer recurrence was not significantly increased (RR 1.21 [95% CI 0.84–1.72]) as compared with patients not receiving bDMARDs, with no heterogeneity between studies ($I^2 = 0\%$, $P = 0.70$) (Figure 4A).

Cervical cancer was reported in 3 studies (25,33,36). Neoplasia developed in 3 of 1,108 patients with a history of cervical intraepithelial neoplasia or cancer of the cervix who were exposed to bDMARDs, with 6 of 2,526 in the control group (no neoplasia in the exposed and unexposed groups in the study by Cordtz et al [33]). For patients with a history of cervical intraepithelial neoplasia or cervical cancer, the risk of cervical cancer (recurrent or new) in patients receiving TNF inhibitors was not significantly increased (RR 0.42 [95% CI 0.01–17.29], $I^2 = 79\%$, $P = 0.03$) as compared with patients receiving no bDMARDs (Figure 4B).

For skin cancers, four studies were selected (26,28,37,38). The RR for risk of recurrence or new cancers (NMSC and melanoma) was 1.32 (95% CI 1.02–1.72) for patients receiving bDMARDs as compared with placebo, with no heterogeneity between studies ($I^2 = 0\%$, $P = 0.04$) (Figure 4C). However, when melanomas were excluded, the risk of NMSC for patients receiving bDMARDs was not significantly increased (RR 1.28 [95% CI 0.96–1.67]; $I^2 = 0\%$, $P = 0.77$) as compared with no bDMARDs (Figure 4B), and the same result was found for patients receiving TNF inhibitors (RR 1.27 [95% CI 0.96–1.68]; $I^2 = 0\%$, $P = 0.09$) (see Supplementary Figure 1, available on the *Arthritis Care &*

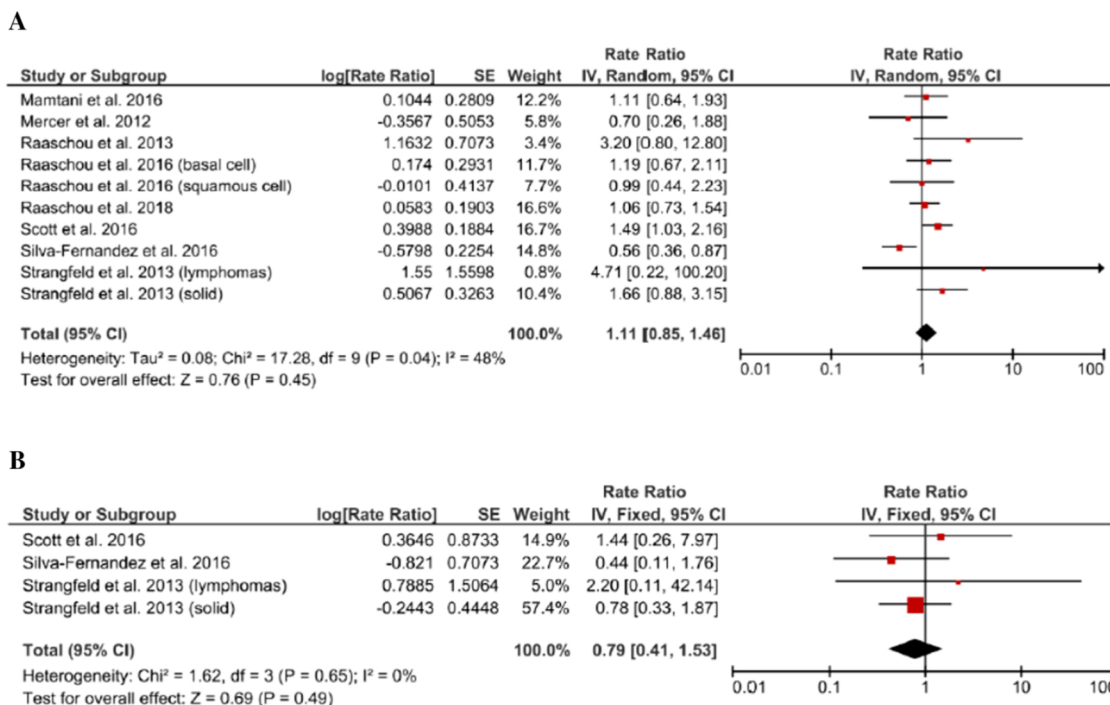


Figure 3. Risk of recurrence or new cancer in patients with rheumatoid arthritis with a history of cancer and receiving anti-tumor necrosis factor (anti-TNF) therapy or rituximab, versus no biologic disease-modifying antirheumatic drugs (bDMARDs). **A**, anti-TNF therapy versus no bDMARDs; **B**, Rituximab versus no bDMARDs. The size of the squares corresponds to the weight of each study. 95% CI = 95% confidence interval; IV = inverse variance.

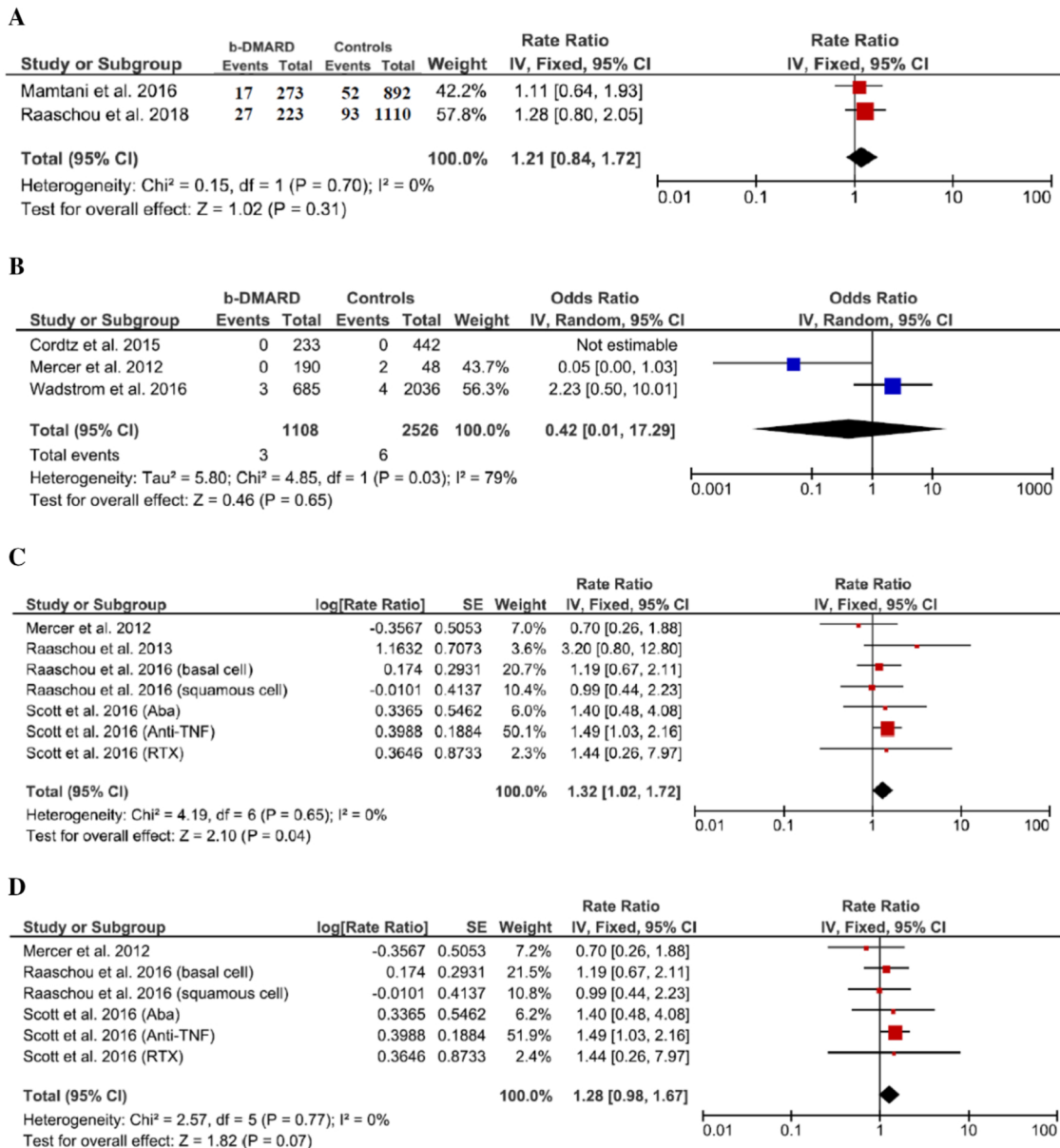


Figure 4. Risk of recurrence or new cancer in patients with rheumatoid arthritis with a history of breast cancer, invasive cervical cancer, or skin cancer and receiving biologic disease-modifying antirheumatic drugs (bDMARDs) versus no bDMARDs. **A**, History of breast cancer; **B**, History of cervical intraepithelial neoplasia or cervical cancer; **C**, History of skin cancer (melanoma and nonmelanoma skin cancers [NMSCs]); and **D**, History of NMSCs. The size of the squares corresponds to the weight of each study. 95% CI = 95% confidence interval; Aba = abatacept; anti-TNF = anti-tumor necrosis factor; IV = inverse variance; RTX = rituximab.

DISCUSSION

In our meta-analysis, the risk of new or recurrent cancer was not significantly increased in RA patients with a history of cancer and receiving bDMARDs versus no bDMARDs. In addition, the risk of new or recurrent cancer was not significantly

increased for patients receiving TNF inhibitors or rituximab versus no bDMARDs. Cervical dysplasia is a precancerous lesion and can be a potential confounding factor. Therefore, we excluded it in the overall risk analysis of recurrent or new cancer. For RA patients with a history of breast cancer, cervical intraepithelial neoplasia, or cervical cancer, the risk of recurrence or new neoplasia was not significantly increased with bDMARDs versus no bDMARDs. In contrast, for RA patients with a history of skin cancer, the risk of recurrence or new cancer was

increased with bDMARDs as compared with no bDMARDs. However, the increased risk was not found when melanoma was excluded. Only 1 study could be included concerning recurrent or new melanoma (28) with a small number of cases and only in situ forms.

Our results are consistent with 2 meta-analyses examining recurrence or new cancer risk in RA and chronic IBD patients with a history of cancer starting treatment with bDMARDs (15,16). Shelton et al (16) showed that the rate of secondary or recurrent cancer was similar among IBD or RA patients receiving anti-TNF therapy (incidence rate [IR] 33.8/1,000 person-years, $I^2 = 73.4\%$), conventional treatment with thiopurine, methotrexate, or azathioprine (IR 36.2/1,000 person-years, $I^2 = 93.6\%$), or without conventional or anti-TNF therapy (IR 37.5/1,000 person-years, $I^2 = 94.3\%$). However, the authors included several small studies, mainly of IBD patients receiving only anti-TNF therapy. These patients present several differences as compared with RA patients: they are often younger, with fewer comorbidities, and with different use of TNF inhibitors. In addition, thiopurine treatment, not used in RA patients, is associated with an increased risk of NMSC (45). The final results of this meta-analysis were also heterogeneous. Micic et al (15) found no increased risk of recurrence or new cancer in patients receiving a TNF inhibitor as compared with the control group (RR 0.68 [95% CI 0.40–1.16] for IBD and 1.06 [95% CI 0.78–1.46] for RA). Our meta-analysis updated the literature review and focused on all bDMARDs in RA (excluding JAK inhibitors because of lack of data), which increased the power of our study. Other strengths are that we selected only registry studies, which allows for longer patient follow-up as compared with randomized studies and a larger numbers of patients. We found homogeneity between studies for most of our results.

However, our study has some limitations. With respect to the other chronic inflammatory arthritis conditions (axial SpA and PsA), the small number of cohort studies and their small size are the main limitations for drawing conclusions. On the basis of current recommendations, patients eligible for treatment with bDMARDs may have less severe cancers and lower risk of recurrence than those receiving no bDMARDs. Most studies did not report a stage classification of cancers. However, in the Raaschou et al cohort (43), baseline characteristics did not differ between cancer stages in the bDMARD and control groups.

Due to lack of data, we could not study the risk of recurrence with rituximab or TNFi treatment according to the subtype of solid cancer or hemopathy. Current recommendations (1,11–13) suggest using rituximab over TNFi for patients with RA and a history of lymphoproliferative disorder. For patients with a history of solid cancer, the 2015 ACR guidelines for RA (46) recommend using the same treatment as in patients without cancer, while the others (1,11) suggest waiting 5 years between cancer remission and the initiation of bDMARDs, except for rituximab treatment. In our meta-analysis, the minimum time between cancer remission and initiation of bDMARDs was difficult to determine because the

duration of cancer remission at the initiation of bDMARDs differed in registries or was not specified.

The use of bDMARDs before inclusion could be a bias in analyzing the data. To avoid this bias, some authors considered in their inclusion criterion the use of bDMARDs for the first time (19,25,26,28,36,37,39,43). Dreyer et al (41) conducted a subanalysis to compare the risk of cancer recurrence between patients receiving bDMARDs before or after the first cancer and found no increased risk of cancer recurrence in each subgroup.

The link between cancer risk and disease activity is now established, particularly for lymphomas. However, the selected cohort studies did not adjust for recurrence risk on RA activity owing to lack of data, which may represent a potential confounding bias. In the cohort study of Silva-Fernández et al (39), at baseline, patients receiving no bDMARDs had lower disease activity than those receiving anti-TNF or rituximab (Disease Activity Score in 28 joints 5.2 versus 6.5–6.6). Thus, patients with higher disease activity could have a higher risk of cancer recurrence with bDMARDs than those with no bDMARDs. However, the authors did not show an increased risk of cancer recurrence. Tobacco is a risk factor for many cancers. However, the study of Silva-Fernández et al (39) is the only one that took this factor into account by adjusting the result. For skin cancers, several risk factors have been identified: ethnic origin (White), country of residence because of sun exposure (47), or treatments (thiopurine, psoralen and ultraviolet A therapy [48,49], steroids [50]). Scott et al (38) and Mercer et al (26) adjusted the results on these risk factors, thereby reducing the confounding bias. Similarly, for cervical cancer or dysplasia, for the 3 selected studies, the results were not adjusted for the most frequent risk factor (human papillomavirus infection). Two studies (19,43) reduced the confounding bias by matching patients receiving bDMARDs to the control population.

Patients receiving bDMARDs have more regular follow-up than those receiving no bDMARDs and therefore more frequent screening for cancer. However, as our study shows, the number of recurrences or new cancers observed in patients receiving bDMARDs was not significantly higher than in the control group, so this follow-up bias is minimal. Finally, although the numbers are larger in this meta-analysis than in randomized studies, subgroup studies could not be conducted for each type of cancer because of rare events and lack of data in the selected studies.

Our study suggests that the risk of recurrent or new cancer is not increased for RA patients with a history of cancer (solid, hemopathy, cervical intraepithelial neoplasia, or NMSC) who receive bDMARDs as compared with patients who receive no bDMARDs. For melanomas, our results do not allow for conclusions because of the small number of retrieved studies, and further studies are needed. For other cancers, cancer in remission and chronic inflammatory arthritis with high activity, the initiation of bDMARDs may be considered without increasing the risk of recurrence or a second cancer.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Szaforz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ROLE OF THE STUDY SPONSOR

AbbVie had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by AbbVie.

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