REVIEW

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Risk of Malignancies in Patients With Rheumatoid Arthritis Treated With Biologic Therapy

A Meta-analysis

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Context Concerns exist regarding the potential development of malignancies in patients with rheumatoid arthritis (RA) who are receiving biologic response modifiers (BRMs).

Objective To assess the risk of malignancy in patients with RA enrolled in randomized controlled trials (RCTs) of BRMs.

Data Sources Electronic databases, conference proceedings, and websites of regulatory agencies were searched for RCTs evaluating abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab in RA from inception through July 9, 2012.

Study Selection Independent selection of studies included RCTs that compared the safety of any BRMs used in RA patients with placebo and/or any traditional disease-modifying antirheumatic drugs with a minimum of 24 weeks of follow-up.

Data Extraction Independent reviewers selected studies and extracted data on quality and outcomes. Pooled estimates and 95% confidence intervals were calculated for each BRM.

Results Sixty-three RCTs with 29 423 patients were analyzed. No statistically significant increased risk of developing malignancy was observed. Of the 29 423 patients, 211 developed a malignancy during the trial (118 solid tumors, 48 skin cancers, 14 lymphomas, 5 hematologic nonlymphomas, and 26 not specified). The incidence rate for any malignancy during the first year of therapy was very low in the BRM plus methotrexate group (0.77%; 95% CI, 0.65%-0.92%), the BRM monotherapy group (0.64%; 95% CI, 0.42%-0.95%), and the controls (0.66%; 95% CI, 0.52%-0.84%). Anakinra plus methotrexate showed lower odds compared with methotrexate alone (Peto odds ratio, 0.11; 95% CI, 0.03-0.45). No statistically significant risk was observed for specific cancer sites, although the Peto odds ratio for lymphoma was 2.1 (95% CI, 0.55-8.4) in patients receiving tumor necrosis factor inhibitors compared with controls.

Conclusion The use of BRMs among patients with RA included in RCTs of at least 6 months' duration was not significantly associated with an increased risk of malignancy compared with other disease-modifying antirheumatic drugs or with placebo.

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RHEUMATOID ARTHRITIS (RA) IS a systemic inflammatory polyarthritis that can lead to significant morbidity, joint deformity, and impaired quality of life[1] and affects approximately 1% of the general population. Treatment with traditional disease-modifying antirheumatic drugs (DMARDs) reduces disease activity, retards joint destruction, and improves patients' quality of life. However, in many patients with active disease, traditional DMARDs fail or are not tolerated.[2]

Biologic response modifiers (BRMs) provide clinically important improvement in patients not responding to traditional DMARDs by targeting specific immune pathways, reducing inflammation, and leading to better control of symptoms and structural damage.[2] In 2010, published data from European and US registries reported that 25% to 56% of patients with RA used BRMs.[3] Available BRMs include tumor necrosis factor (TNF) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), an interleukin 1 receptor antagonist (anakinra), B-cell–depleting anti-CD20 antibodies (rituximab), a selective costimulation modulator inhibiting T-cell activation by binding to

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CD80 and CD86 (abatacept), and an interleukin 6 inhibitor (tocilizumab).

Because these biologic agents interfere with the immune system, concerns exist regarding their safety, specifically with respect to infections and malignancies. The US Food and Drug Administration (FDA) has recommended adding a warning label concerning risk of malignancy to all TNF inhibitors because of the increase in cases of spontaneous lymphoma in children and adolescents in the Adverse Event Reporting System database.[4]

Since 2005, conflicting data have existed associating TNF inhibitors with an increased risk of developing certain types of malignancies. Most observational studies have found increased risk of malignancies ranging across studies, with relative risks (RRs) of 0.7 to 2.7 for all types of malignancies, 1.1 to 5.0 for lymphoma, and 1.1 to 1.5 for nonmelanoma skin cancer. Eleven meta-analyses of randomized controlled trials (RCTs) have been performed evaluating the risk of malignancy in patients with RA undergoing treatment with TNF inhibitors.[5-15] This is the first systematic review, to our knowledge, evaluating the risk of developing any type of malignancy in patients with RA only and providing data on all 9 approved BRMs.

METHODS

For this systematic review, we followed Cochrane Collaboration methods.[16]

Data Sources and Searches

A comprehensive search of the literature was performed by an experienced medical librarian and information specialist (S.F.) with input from the study team, using the following databases: MEDLINE, Cochrane Library, EMBASE (through SCOPUS), Web of Science, and electronic abstract databases of the annual scientific meetings of both the American College of Rheumatology and the European League Against Rheumatism. We searched all databases from inception to June 6, 2011. Ovid Auto Alerts were set up to provide weekly updates of new literature until July 09, 2012. Limits included human subjects and English, French, and Spanish languages. The search strategies for each electronic database are reported in eAppendix 1, eAppendix 2, and eAppendix 3 (available at http://www.jama.com). Websites and reference lists from systematic reviews and RCTs were hand-searched for additional citations not retrieved through electronic databases.

Study Selection

Study selection was performed by 4 pairs of independent reviewers (M.A.L.-O. and J.P.C., J.A.M.-L. and M.R.G.-C., E.N.P. and M.E.S.-A., and M.A.L.-O. and J.H.T.). Disagreements were clarified by consensus and, when needed, an external reviewer acted as an adjudicator. κ Agreement scores were calculated for each pair of reviewers.

To be eligible for inclusion, trials had to (1) compare the safety of any of the BRMs (abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, and/or tocilizumab) against placebo and/or any DMARD; (2) include only patients with RA; and (3) report a minimum of 24 weeks of follow-up. We excluded studies with no descriptions of adverse events and follow-up reports of original publications (parent studies) that were open labeled without a control group.

Data Extraction and Quality Assessment

Data extraction was done independently by 2 reviewers (M.A.L.-O. and E.N.P.) and cross-checked by 2 additional reviewers (J.P.C. and J.H.T.). Discrepancies were solved by consensus, and there was an adjudicator (M.E.S.-A.) in case of persistent disagreement. From each selected trial, we collected general information, study, population, and intervention characteristics. Primary outcome data included number and type of malignancies. We contacted all corresponding authors and pharmaceutical companies to obtain data for trials that did not include number of malignancies observed.

Risk of bias of included studies was assessed by 2 reviewers (M.A.L.-O. and E.N.P.). Trials were appraised on sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases (baseline imbalance, carryover, funding).[16] Each criterion was judged using the categories of yes (low risk of bias), no (high risk of bias), and unclear (lack of information or uncertainty about the potential for bias). A summary score was then derived whereby low risk of bias was given to studies with bias unlikely altering the results; unclear risk of bias was given to studies raising doubt about the results; and high risk of bias was given to studies that weakened confidence in the results.

Data Synthesis and Analysis

Our meta-analysis was performed using RevMan version 5.0.21 (Cochrane IMS) and Comprehensive Meta-analysis version 2.2.055. Data were combined and expressed as both Peto odds ratios (ORs) and RRs with their associated 95% confidence intervals. Although we show both measures of association, the Peto OR is preferred for uncommon events, and corrections for 0 cell counts in a single group are not necessary.[16,17] Our numerators were the number of patients with malignancy reported in each trial. For the denominator, we considered all patients reported for safety in the original trial; for some trials, this represented the intention-to-treat population, but for most trials, it was patients exposed to at least 1 dose of the study drug as proposed by Bongartz et al.[5]

For the Peto ORs and RRs, 0-total-event trials (no events in either the intervention or control group) are automatically excluded because the studies do not provide any indication of either the direction or the magnitude of the relative treatment.[16] We analyzed the data adding 0-total-event trials with a continuity correction estimate of the

OR. Trials that did not report malignancies were included in the meta-analysis with a 0 in the numerator. For correction, a constant value of 0.5 was added to all cells of the 2×2 contingency table to provide a more conservative estimate of effect size.[18]

Heterogeneity of the data was formally tested. We used random-effects models to calculate a more conservative combined estimate of RR. Subgroup analyses were performed to check whether BRM monotherapy or combination therapy with traditional DMARDs or based on follow-up (24, 52, 104, and 156 weeks) would substantially change the findings. Sensitivity analyses were performed for intention-to-treat vs completer samples, quality of the trials, drug dosages, duration of the exposure (<1 year or ≥1 year), and excluding trials that did not report malignancies or that used rescue alternatives (before 24 weeks) and placebo-controlled trials with no concomitant treatment. Publication bias was assessed and quantified using funnel plots, the Orwin fail-safe N, the Duval and Tweedie trim and fill, and the Egger test. Results were analyzed both at a 2-sided α level of significance of .05 and with a Bonferroni correction to control for multiple testing of various BRMs (significance was set at α/κ).

RESULTS

Study Selection

We identified 16 587 unique citations located through databases, handsearching, and conference proceedings. Our first selection round resulted in 2114 records potentially relevant to our topic. Of those, 395 were retrieved in full article form for further reading. Of the 395 articles, 71 publications[19-89] reporting on 63 distinct trials met inclusion for our systematic review (eFigure 1). κ Coefficients for selection ranged between 0.96 and 0.99. Also, no evidence of publication bias was observed. eFigure 2 shows the funnel plots. Additionally, the Orwin fail-safe N and the Duval and Tweedie trim and fill were performed with no changes in the effect sizes. The Egger test indicated no publication bias in all studies for all comparisons.

Study Characteristics

eTable 1 shows the characteristics of included studies. Most trials were randomized, double-blind, and placebo-controlled. Randomization ratios ranged from 1:1 to 3:2.

Thirty-six trials had more than 1 treatment group and 1 placebo group. Follow-up ranged from 24 to 156 weeks (eTable 2 and eTable 3). There were multiple dosages for each BRM. Dosages for abatacept were 2 to 10 mg/kg every 4 weeks; adalimumab, 20, 40, or 80 mg every other week and 20 or 40 mg every week; anakinra, 30 to 150 mg or 0.04 to 1 mg/kg daily; certolizumab, 200 or 400 mg every 2 or 4 weeks; etanercept, 10 or 25 mg twice weekly; golimumab, 50 or 100 mg every 2 or 4 weeks or 2 or 4 mg/kg every 12 weeks; infliximab, 1, 3, 5, 6, or 10 mg/kg every 4 or 8 weeks; rituximab, 500 or 1000 mg at day 0 and 15 mg every 6 or 12 months; and tocilizumab, 2, 4, or 8 mg/kg every 4 weeks. Thirty-four studies included a rescue regimen for nonresponders in the control group by increasing control dosages, changing to other traditional DMARDs, withdrawing from the study, or administering the study BRMs.

Sample sizes ranged from 20[19] to 1399.[20] eTable 4 describes the characteristics of patients included in each trial. All trials were reported as multicenter trials without further specific information regarding the setting. Sixty-six percent (42/63) were reported as multinational studies.

Sixty-three trials with 29 423 patients were included in this analysis. A total of 15 989 were assigned to BRMs plus methotrexate (and/or other DMARDs), 3615 to BRMs alone, and 9819 to control groups. Four trials had comparisons between BRMs: Genovese et al[21] compared anakinra plus etanercept vs etanercept; Weinblatt et al[22] compared abatacept plus etanercept vs etanercept; Greenwald et al[23] compared rituximab plus etanercept or adalimumab vs etanercept or adalimumab; and van Vollenhoven et al[24] compared atacicept vs adalimumab. Furthermore, the ATTEST trial[25] was a head-to-head trial comparing infliximab vs abatacept vs control, and we only analyzed each group vs control. For 50 trials, to be eligible participants had to have active disease and failure of traditional DMARDs (15 trials also required a previous failure of TNF inhibitors), and 13 trials included patients naïve to methotrexate and/or other DMARDs. The majority of patients were white (79%) and women (76%). The mean age ranged from 44.8 to 56.5 years. Mean disease duration ranged from 0.35 to 13 years.

Eleven trials did not mention malignancies in their reported adverse events, and the corresponding authors and sponsors were contacted to retrieve the data.[19,26-35] Listed primary end points were efficacy, safety, and radiographic outcomes in 6 trials; efficacy and safety in 23 trials; efficacy and radiographic outcomes in 7 trials; efficacy and job loss in 1 trial; efficacy alone in 16 trials; safety alone in 7 trials; radiographic outcomes alone in 2 trials; and work disability in 1 trial.

Risk of Bias in Included Studies

Only 19 trials clearly reported adequate sequence generation and allocation concealment by assigning each patient a unique sequential number using a central (interactive voice) randomization system, and the randomization schedules were generated and kept sealed until the unblinding of the study. Forty-three trials did not mention allocation concealment in the published article. One study reported adequate allocation concealment, but no information was provided on how randomization was performed. Five trials were unblinded.[26,36-40] Nishimoto et al[41] conducted a reader-blinded study and van Vollenhoven et al[24] included an open-label adalimumab group.

The completion rates ranged from 49% to 94% in the BRM-monotherapy groups, from 58% to 99% in the BRM combination therapy groups, and from 5% to 100% in the control groups; ad-

verse events were cause for discontinuation in 23%, 33%, and 18%, respectively; and lack of efficacy was reported for 37%, 29%, and 50%, respectively. There was little risk of bias due to selective reporting. Fifty-six trials were sponsored by a pharmaceutical company and 3 trials did not disclose the source of funding. The remaining 4 were funded by the French Society of Rheumatology,[36] the Dutch College of Health Insurances,[37,38] the Swedish Rheumatism Association,[40] or the National Center for Research Resources[30]; however, drugs were provided free of charge by industry.

Malignancies

We obtained additional information on malignancies from the authors/sponsors for 9 trials.[26-32,34,35] An additional 2 trials did not report malignancies, but the authors did not provide additional data.[19,33] Of the 29 423 patients, 211 developed a malignancy during the trial (0.72%; 95% CI, 0.63%-0.82%): 23 of 3615 patients in the BRM monotherapy group (0.64%; 95% CI, 0.42%-0.95%), 123 of 15 989 patients in the BRM combination therapy group (0.77%; 95% CI, 0.65%-0.92%), and 65 of 9819 patients in the control group (0.66%; 95% CI, 0.52%-0.84%). eTable 2 and eTable 3 show the malignancies reported in each trial for TNF inhibitors and other BRMs, respectively.

Of the 211 malignancies, 118 were solid tumors (ie, adrenal, bladder, breast, cholangiocarcinoma, fibrosarcoma, gastrointestinal, hepatic, leiomyosarcoma, liposarcoma, lung, ovarian, pancreatic, prostate, renal, testicular, thyroid, tongue, uterine), 48 were skin cancer (ie, basal cell, squamous cell, and 4 melanomas), 14 were lymphomas, 26 were not specified, and 5 were hematologic nonlymphoma (ie, multiple myeloma, leukemia). TABLE 1 and TABLE 2 show the risk of malignancy for TNF inhibitors and other BRMs. We show all 3 risk estimates: Peto OR, RR, and continuity correction for 0-total-event trials, but focus on the Peto ORs because they are the most appropriate for events occurring with low frequency. For each individual BRM, Peto ORs ranged from 0.11 to 7.4. The only statistically significant increase in risk of malignancy we observed was for the combined TNF inhibitor plus methotrexate group vs controls (Peto OR, 2.1; 95% CI, 1.1-3.9) at 52 weeks (Table 1); with an attributable risk percentage of 52% (95% CI, 9%-74%; P = .005). However, with random effects, the model was not significant (RR, 1.8; 95% CI, 0.82-3.8). No differences were observed when TNF inhibitors alone were compared with controls (methotrexate or DMARDs alone) (Peto OR, 0.98; 95% CI, 0.51-1.9). Individually, none of the TNF inhibitors showed a statistically significant risk. For the non-TNF inhibitors, non–statistically significant differences were observed in most instances. Anakinra plus methotrexate had statistically significantly lower odds of malignancy compared with methotrexate alone (Peto OR, 0.11 [95% CI, 0.03-0.45]; prevented risk percentage, 89% [95% CI, 55%-97%]; and absolute risk reduction, 9 [95% CI, 2-21] per 1000 patients) at 24 weeks (Table 2).

The FIGURE shows the occurrence of melanoma and nonmelanoma skin cancer, lymphoma, solid tumors combined, other hematologic, and unspecified malignancies in patients with RA treated with BRMs. Peto ORs ranged between 0.01 (95% CI, 0.00-0.94) for developing lymphoma with anakinra therapy to 5.7 (95% CI, 0.31-104.9) for other hematological malignancies with infliximab therapy (eTable 5). Patients treated with anakinra had lower odds of developing nonmelanoma skin cancer (Peto OR, 0.06; 95% CI, 0.00-0.94). No other pooled results were statistically significant. The risk of lymphoma with TNF inhibitors was doubled but did not reach statistical significance (Peto OR, 2.1; 95% CI, 0.55-8.4).

Sensitivity Analysis

Using the continuity correction, results were similar to the Mantel-Haenszel RR. Analyzing by intention to treat, quality of the trials, dosage, drug exposure (≤1 year or >1 year), no rescue therapy (before 24 weeks), or excluding placebo-controlled trials with no concomitant treatment had no effect on our results (eTable 6 and eTable 7). When analyzing the data excluding trials with no report of malignancy using the continuity correction, the only significant increase, in risk of malignancy observed for the combined TNF inhibitor plus methotrexate group vs controls, remained significant (Peto OR, 2.0; 95% CI, 1.1-3.8 at 52 weeks) but with no increased risk at other time points. There were no statistically significant differences for any of the analyses when applying Bonferroni correction.

COMMENT

To our knowledge, this is the largest systematic review and meta-analysis examining the risk of malignancy in patients with RA receiving BRMs in RCTs. We pooled results from 63 RCTs including 29 423 patients, followed up for at least 24 weeks, to estimate the risk of developing cancer among users of BRMs compared with controls (ie, traditional DMARDs, placebo, or a BRM). There was no statistically significant increased risk of any type of cancer with use of BRMs vs controls. The only increased risk of malignancy we observed was in patients with RA treated with TNF inhibitors plus methotrexate at 52 weeks, for all cancers combined, with patients receiving these agents having twice the risk of malignancy than controls. However, this increase was not observed at other time points (24, 104, or 156 weeks) or with monotherapy.

There are various published reports reviewing the risk of malignancy in patients with RA treated with TNF inhibitors.[5,6,90-93] Ours are in contrast with the findings published by Bongartz et al,[5] who reported a dose-dependent increased risk of malignancies in patients with RA treated with a TNF inhibitor. In a follow-up analysis of etanercept RCTs, an increased risk of 1.8 was observed but did not reach

Table 1. Risk of Malignancy (All Types Combined) in Patients Treated With TNF Inhibitors

Intervention	No. of Participants (No. of Studies)	Cumulative Malignancy Incidence, No. With Malignancy/No. Included in Safety Analysis		Peto OR (95% CI)	Relative Risk (95% CI)[a]	Continuity Correction, Peto OR (95% CI)[b]
		BRMs	Control			
Adalimumab alone vs placebo or methotrexate[c]						
At 24 weeks[42,43]	896 (2)	4/699	3/197	0.28 (0.05-1.7)	0.32 (0.02-4.6)	0.28 (0.05-1.7)
At 104 weeks[44]	531 (1)	4/274	4/257	0.94 (0.23-3.8)	0.94 (0.24-3.7)	0.94 (0.23-3.8)
Pooled[d]	1427 (3)	8/973	7/454	0.60 (0.20-1.8)	0.61 (0.16-2.3)	0.60 (0.20-1.8)
Adalimumab + DMARD[c] vs placebo + methotrexate						
At 24 weeks[24,45-47]	1190 (4)	2/671	0/519	5.5 (0.27-111.1)	1.6 (0.17-15.7)	2.2 (0.28-16.5)
At 52 weeks[36,48,49]	832 (3)	6/527	0/305	5.3 (0.99-28.5)	4.6 (0.56-37.0)	4.1 (0.87-19.1)
At 104 weeks[44]	525 (1)	2/268	4/257	0.49 (0.10-2.4)	0.48 (0.09-2.6)	0.49 (0.10-2.4)
Pooled[d]	2547 (8)	10/1466	4/1081	1.8 (0.61-5.4)	1.3 (0.41-4.0)	1.6 (0.61-4.3)
Certolizumab alone vs placebo						
At 24 weeks[50]	220 (1)	0/111	0/109	NE	NE	0.98 (0.02-49.5)
Certolizumab + methotrexate vs placebo + methotrexate						
At 24 weeks[51,52]	862 (2)	2/618	1/244	0.44 (0.03-7.4)	0.51 (0.05-5.5)	0.58 (0.06-5.7)
At 52 weeks[53]	980 (1)	11/781	1/199	2.1 (0.51-8.7)	2.8 (0.36-21.6)	2.1 (0.51-8.7)
Pooled[d]	1842 (3)	13/1399	2/443	1.5 (0.44-5.5)	1.3 (0.24-7.3)	1.5 (0.44-4.9)
Etanercept alone vs placebo or DMARD[c]						
At 24 weeks[33,54]	472 (2)	0/272	0/200	NE	NE	0.73 (0.04-12.4)
At 52 weeks[55]	632 (1)	5/415	2/217	1.3 (0.27-6.2)	1.3 (0.26-6.7)	1.3 (0.27-6.2)
At 104 weeks[56,57]	153 (1)	2/103	0/50	4.5 (0.23-86.5)	2.5 (0.12-50.1)	4.5 (0.23-86.5)
At 156 weeks[58]	451 (1)	5/223	2/228	2.4 (0.55-10.8)	2.6 (0.50-13.0)	2.4 (0.55-10.8)
Pooled[d]	1708 (5)	12/1013	4/695	2.0 (0.73-5.5)	1.9 (0.65-5.6)	1.8 (0.69-4.7)
Etanercept + DMARD vs placebo + methotrexate						
At 24 weeks[35]	89 (1)	0/59	0/30	NE	NE	0.49 (0.01-30.8)
At 52 weeks[59]	542 (1)	4/274	4/268	0.98 (0.24-4.0)	0.98 (0.25-3.9)	0.97 (0.24-3.9)
At 104 weeks[56,57]	151 (1)	0/101	0/50	NE	NE	0.47 (0.01-30.2)
At 156 weeks[58,60,61]	459 (1)	5/231	2/228	2.4 (0.53-10.5)	2.5 (0.48-12.6)	2.4 (0.53-10.5)
Pooled[d]	1241 (4)	9/665	6/576	1.5 (0.53-4.1)	1.4 (0.50-4.1)	1.3 (0.50-3.4)
Golimumab alone vs placebo + methotrexate						
At 24 weeks[62,63]	583 (2)	2/290	3/293	0.67 (0.12-3.9)	0.78 (0.08-7.2)	0.67 (0.12-3.9)
At 52 weeks[64]	388 (1)	2/259	2/129	0.47 (0.06-3.8)	0.50 (0.07-3.5)	0.47 (0.06-3.8)
Pooled[d]	971 (3)	4/549	5/422	0.58 (0.15-2.2)	0.65 (0.17-2.5)	0.58 (0.15-2.2)
Golimumab + methotrexate vs placebo + methotrexate						
At 24 weeks[62,65,66]	1247 (3)	5/799	4/448	0.68 (0.17-2.7)	0.69 (0.18-2.6)	0.68 (0.17-2.7)
At 52 weeks[63,64]	554 (2)	6/391	2/163	1.1 (0.22-5.4)	0.81 (0.16-4.1)	1.1 (0.22-5.4)
Pooled[d]	1801 (5)	11/1190	6/611	0.83 (0.29-2.4)	0.73 (0.26-2.1)	0.83 (0.30-2.4)
Infliximab alone vs placebo + methotrexate						
At 24 weeks[67]	58 (1)	0/44	0/14	NE	NE	0.26 (0.003-24.4)
Infliximab + methotrexate vs placebo + DMARD[c]						
At 24 weeks[25,67]	332 (2)	2/208	1/124	1.3 (0.13-13.4)	1.3 (0.12-14.5)	0.95 (0.12-7.5)
At 52 weeks[39,68,69]	2166 (3)	12/1485	1/681	3.1 (0.95-9.9)	3.8 (0.71-20.8)	3.0 (0.96-9.2)
At 104 weeks[19,37,38,40,70-73]	1214 (4)	11/608	8/606	1.2 (0.40-3.4)	1.2 (0.32-4.6)	1.2 (0.41-3.3)
Pooled[d]	3712 (9)	25/2301	10/1411	1.8 (0.83-3.7)	1.8 (0.68-4.6)	1.7 (0.80-3.4)
All TNF inhibitors alone vs placebo or DMARD[c]						
At 24 weeks[33,42,43,50,54,62,66,67]	2229 (8)	6/1416	6/813	0.44 (0.12-1.6)	0.53 (0.12-2.3)	0.49 (0.17-1.4)
At 52 weeks[55,64]	1020 (2)	7/674	4/346	0.90 (0.26-3.1)	0.88 (0.25-3.1)	0.90 (0.26-3.1)
At 104 weeks[44,56,57]	684 (2)	6/377	4/307	1.2 (0.35-4.4)	1.1 (0.32-3.9)	1.2 (0.35-4.4)
At 156 weeks[58]	451 (1)	5/223	2/228	2.4 (0.55-10.8)	2.6 (0.50-13.0)	2.4 (0.55-10.8)
Pooled[d]	4384 (13)	24/2690	16/1694	0.98 (0.51-1.9)	1.0 (0.51-1.9)	0.94 (0.51-1.8)
All TNF inhibitors + DMARD vs DMARD[c]						
At 24 weeks[24,25,35,45-47,51,52,62,65-67]	3720 (12)	11/2355	6/1365	0.93 (0.34-2.6)	0.85 (0.33-2.2)	0.87 (0.36-2.1)
At 52 weeks[36,39,48,49,53,59,63,64,68,69]	5075 (10)	39/3458	8/1617	2.1 (1.1-3.9)[e]	1.8 (0.82-3.8)	2.0 (1.1-3.8)[e]
At 104 weeks[19,37,38,40,44,56,57,70-73]	1890 (6)	13/977	12/913	0.89 (0.36-2.2)	0.85 (0.30-2.4)	0.87 (0.37-2.0)
At 156 weeks[58,60,61]	459 (1)	5/231	2/228	2.4 (0.53-10.5)	2.5 (0.48-12.6)	2.4 (0.53-10.5)
Pooled[d]	11 144 (29)	68/7021	28/4123	1.5 (0.95-2.3)	1.3 (0.77-2.1)	1.4 (0.91-2.1)

Abbreviations: BRM, biologic response modifier; DMARD, disease-modifying antirheumatic drug; NE, not estimable; TNF, tumor necrosis factor.
[a] A random-effects model was used for all comparisons.
[b] For continuity correction, 0.5 was added to each cell of the 2 × 2 contingency table[18] only for 0-total-event trials (no events in either the intervention or control group).
[c] Patients in the control group received (1) placebo or methotrexate or (2) placebo or traditional DMARDs.
[d] All time points included.
[e] $P \leq .05$.

statistical significance. In a more recent meta-analysis by Askling et al[94] including RCTs of TNF inhibitors, using patient-level data and Bayesian methods, no increased short-term risk of cancer other than nonmelanoma skin cancer was found. This analysis, however, included patients with any condition, not just RA, and did not categorize the analyses with respect to addition of other DMARDs (eg, methotrexate) in the treatment or control groups.

In observational studies, the association between malignancies and BRMs has varied. Wolfe and Michaud[95] examined the incidence of cancer among 13 001 patients with RA, about 50% of them treated with BRMs, during 49 000 patient-years of observation, observing a small but significant increase in the risk of both nonmelanoma and melanoma skin cancers (ORs, 1. 5 and 2.3, respectively). Wolfe and Michaud[96] and Geborek et al[97] also documented increased risk of lymphoma in patients with RA compared with the general population, with greater risk in patients treated with TNF inhibitors. Others have not found significant increases in the risk of hematologic malignancies and common solid tumors in BRM users.[8,98,99] The reason for the observed discrepancies are somewhat unclear but could be attributed to some degree to the selection of the control population in these observational studies. Unlike clinical

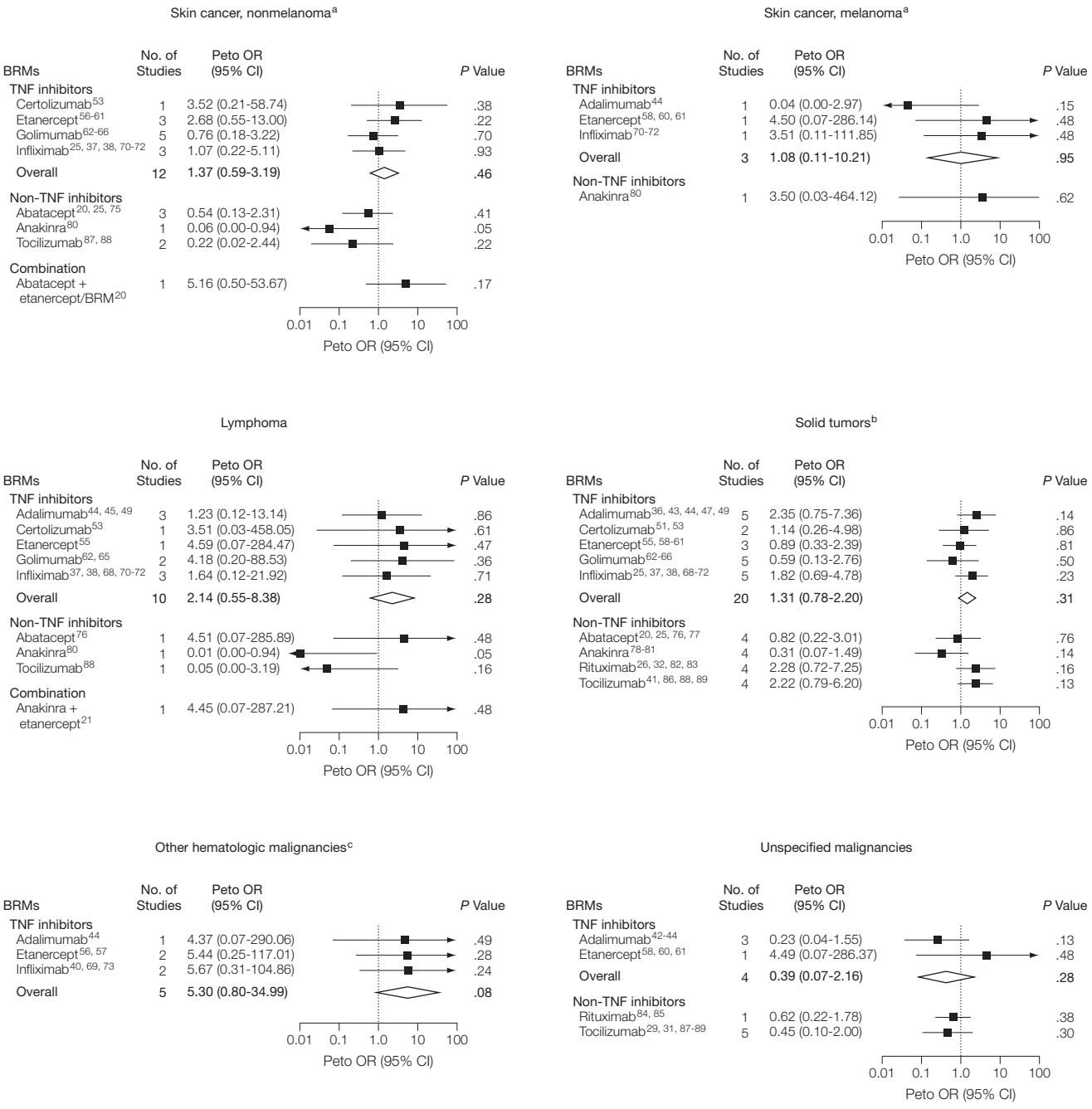
Table 2. Risk of Malignancy (All Types Combined) in Patients Treated With Non–TNF Inhibitor BRMs

Intervention	No of Participants (No. of Studies)	Cumulative Malignancy Incidence, No. With Malignancy/No. Included in Safety Analysis		Peto OR (95% CI)	Relative Risk (95% CI)[a]	Continuity Correction, Peto OR (95% CI)[b]
		BRMs	Control			
Abatacept alone vs placebo alone						
At 32 weeks[74]	56 (1)	1/28	0/28	7.4 (0.15-372.4)	3.0 (0.13-70.6)	7.4 (0.15-372.4)
Abatacept + DMARD vs placebo + DMARD						
At 24 weeks[25,30,75]	996 (3)	1/634	1/362	0.70 (0.04-11.7)	0.71 (0.04-11.2)	0.60 (0.08-4.5)
At 52 weeks[20,76,77]	2435 (3)	9/1545	7/890	0.64 (0.23-1.8)	0.65 (0.25-1.7)	0.64 (0.23-1.8)
Pooled[c]	3431 (6)	10/2179	8/1252	0.65 (0.24-1.7)	0.66 (0.27-1.6)	0.63 (0.25-1.6)
Anakinra alone vs placebo alone						
At 24 weeks[78]	472 (1)	2/351	0/121	3.9 (0.16-92.3)	1.7 (0.08-35.8)	3.8 (0.16-92.3)
Anakinra + methotrexate vs placebo + methotrexate						
At 24 weeks[79-81]	2319 (3)	5/1711	7/608	0.11 (0.03-0.45)[d]	0.22 (0.07-0.66)[d]	0.11 (0.03-0.46)[d]
Rituximab alone vs placebo + methotrexate						
At 48 weeks[27]	80 (1)	0/40	0/40	NE	NE	1.0 (0.02-50.4)
Rituximab + DMARD vs placebo + methotrexate						
At 24 weeks[26,28,32,82,83]	2066 (5)	11/1349	2/717	2.3 (0.72-7.2)	1.5 (0.38-6.1)	2.0 (0.66-6.2)
At 48 weeks[27]	121 (1)	0/81	0/40	NE	NE	0.47 (0.01-30.2)
At 104 weeks[84,85]	748 (1)	9/498	7/250	0.62 (0.22-1.8)	0.65 (0.24-1.7)	0.62 (0.22-1.8)
Pooled[c]	2935 (7)	20/1928	9/1007	1.1 (0.51-2.4)	0.86 (0.39-1.9)	1.1 (0.50-2.2)
Tocilizumab alone vs placebo + methotrexate						
At 24 weeks[34,86]	697 (2)	0/349	1/348	0.13 (0.00-6.7)	0.33 (0.01-8.0)	0.37 (0.02-6.0)
At 52 weeks[41]	302 (1)	3/157	0/145	6.9 (0.71-67.3)	6.5 (0.34-124.2)	6.9 (0.71-67.3)
Pooled[c]	999 (3)	3/506	1/493	2.6 (0.36-18.3)	1.6 (0.08-29.2)	2.1 (0.37-12.4)
Tocilizumab + methotrexate vs placebo + methotrexate						
At 24 weeks[29,31,87,88]	2950 (4)	6/1967	8/983	0.33 (0.11-1.0)	0.41 (0.14-1.2)	0.33 (0.11-1.0)
At 52 weeks[89]	1190 (1)	9/798	1/392	2.9 (0.76-10.7)	4.4 (0.56-34.8)	2.9 (0.76-10.7)
Pooled[c]	4140 (5)	15/2765	9/1375	0.81 (0.35-1.9)	0.65 (0.18-2.2)	0.81 (0.35-1.9)
Biologic combinations						
Abatacept + etanercept or BRM vs placebo + etanercept or BRM[e]						
At 52 weeks[20,22]	288 (2)	3/188	0/100	5.2 (0.50-53.7)	4.4 (0.23-83.3)	2.8 (0.36-22.1)
Anakinra + etanercept vs placebo + etanercept						
At 24 weeks[21]	242 (1)	1/162	0/80	4.5 (0.07-287.2)	1.5 (0.06-36.2)	4.5 (0.07-287.2)
Rituximab + methotrexate + etanercept or adalimumab vs placebo + methotrexate + etanercept or adalimumab[e]						
At 24 weeks[23]	51 (1)	0/33	0/18	NE	NE	0.50 (0.01-30.9)

Abbreviations: BRM, biologic response modifier; DMARD, disease-modifying antirheumatic drug; NE, not estimable; TNF, tumor necrosis factor.
[a] Random-effects model was used for all comparisons.
[b] For continuity correction, 0.5 was added to each cell of the 2 × 2 contingency table[18] only for 0-total-event trials (no events in either the intervention or control group).
[c] All time points included.
[d] $P \leq .05$.
[e] Patients in the control group received 1 BRM (etanercept, adalimumab, or another BRM). Patients in the intervention group could receive a combination of 2 BRMs (etanercept, adalimumab, or another BRM).

trials, cohort studies may be subject to confounding by indication, and the controls, patients with RA not receiving BRMs, might be very different with respect to relevant factors compared with those receiving therapy. Conceivably, patients with a personal or family history of cancer or other important risk factors might be less

Figure. Effect of BRMs on Occurrence of Specific Types of Cancer in Patients With Rheumatoid Arthritis



BRM indicates biologic response modifier; OR, odds ratio; TNF, tumor necrosis factor. Numbers of patients included in each comparison are reported in eTable 5. Diamonds represent pooled effect estimates with 95% CIs for all TNF inhibitors.

[a] For infliximab, 1 patient reported both squamous cell carcinoma and melanoma.

[b] Adrenal, bladder, breast, cholangiocarcinoma, fibrosarcoma, gastrointestinal, hepatic, leiomyosarcoma, liposarcoma, lung, ovarian, pancreatic, prostate, renal, testicular, thyroid, tongue, and uterine.

[c] Multiple myeloma and leukemia.

likely to receive BRMs and could have a higher incidence of cancer than the population with RA at large, therefore decreasing the risk that could be attributable to the intervention when included as controls. Of interest, Carmona et al[100] found no increase in the overall risk of malignancy in patients exposed to TNF inhibitors compared with controls. However, when examining the risk factors for cancer in these patients, age, treatment with methotrexate, treatment with steroids, and chronic obstructive pulmonary disease were significantly associated with developing a malignancy. Despite being subject to bias, cohort studies are needed to evaluate long-term exposures and cumulative effects.

The available data appear to suggest that there is no cumulative risk over time, but these data are also subject to attrition bias. Clinical trials, however, are less subject to bias and, in the context of malignancies, are appropriate to evaluate rapid development of cancer and possibly increased risk of progression of existing occult disease. While trials in RA are relatively short and cannot evaluate risk over long-term exposure, as observational studies do, we thought there was a need to conduct an updated meta-analysis of RCTs because of the older reports of the possible increase in malignancies[5] and the more recent FDA advisory for TNF inhibitors, mostly based on studies in children.[4] Furthermore, Brown et al[101] reviewed MedWatch reports of 26 cases of lymphoproliferative disorders that occurred following treatment with either etanercept or infliximab and found that more than half of the patients who developed lymphoma did so within 8 weeks after initiation of TNF inhibitors. In addition, the concerns in patients receiving BRMs are not only for de novo development of cancer but also for potential acceleration of progression of an occult, not yet diagnosed malignancy. Nannini et al[8] conducted a qualitative systematic review of RCTs in patients with RA, psoriatic arthritis, and ankylosing spondylitis and found that 26% of cancers occurred within 12 weeks of onset of therapy, suggesting that these were preexisting occult malignancies.

Overall, our results show no increased risk of malignancy in RCTs of at least 24 weeks' duration. There was only a small increase in risk at 52 weeks for patients receiving TNF inhibitors in combination with methotrexate, but this effect was not consistent throughout all 3 analytic approaches, in patients receiving TNF inhibitors as monotherapy, or at other time points. Furthermore, the incidence rate for any malignancy was very low in both the TNF inhibitor plus methotrexate group and in controls (1.1% vs 0.5%, respectively). The absolute risk was therefore quite small at 6 per 1000 patients with a number needed to harm of 159.

Other biologic agents did not show clear trends of an increase in malignancy. In fact, anakinra showed a statistically significant decrease in risk. Interestingly, laboratory data suggest that interleukin 1 may have carcinogenetic effects that could be exerted through their inflammatory properties or through direct stimulus of tumor growth.[102-104] Anakinra has been shown to inhibit tumor growth in mouse models.[102] Furthermore, preliminary epidemiologic data show an association between interleukin 1 expression and cancer progression.[105] We cannot discard the possibility that the protective effect of anakinra could be partially due to a higher-than-usual malignancy rate in controls. However, our data are based on a pooled estimate of 63 RCTs, with an expectation that baseline expected rates for malignancy before intervention were similar for active and control groups.

Our study has several limitations related to the quality of data in the original sources. First, in this review we could not adequately assess risk of bias in some instances because the publications did not provide enough details in their reports. Data necessary for further analysis and information on type of malignancy, time point of occurrence, and history of cancer were sometimes lacking; however, we successfully contacted corresponding authors and sponsors to retrieve data on most studies (61/63).

Second, owing to the unavailability of translators, we included only trials published in English, French, or Spanish. There is a concern that articles reporting positive results are more likely to be published in English, which may have led to underestimation in our results. However, our analysis did not find evidence of publication bias.

Third. our data abstraction was not blinded, and failure to blind could lead to a bias. While there is some limited evidence that blinding in data abstraction may not alter the results of a meta-analysis, this methodological issue has not been entirely resolved.[106-108] One of the data extractors was not familiar with the study area and, in addition, data extraction was cross-checked independently by 2 investigators to decrease potential biases related to lack of blinding.

Fourth, most of the studies were funded by pharmaceutical companies, which can also affect outcomes. There is evidence that industry-sponsored trials may overestimate the treatment effect and could possibly also overestimate safety.[109] The effect of funding bias could not be explored because the 4 trials for which funding was not reported evaluated 3 different drugs (adalimumab, infliximab, and abatacept). To minimize the limited statistical power to detect differences between treatments for rare events, we combined different agents with a similar mode of action (all TNF inhibitors), and the validity of pooling did not appear to be compromised because studies were homogeneous (I^2=0%).

Fifth, data from RCTs are not always generalizable; the superior internal validity can be good to establish causality, but their strict selection criteria can compromise generalizability.[110] Registry data can overcome this problem with results more applicable to the "real world." However, community-based observational data are generally very complex and can be subject to confounding bias.

Overall, our findings do not support an increased risk of malignancy for patients with RA receiving BRMs in RCTs of at least 24 weeks' duration. Additional systematic reviews of observational studies are needed to establish risk in the longer term. Although the findings suggest that BRMs may be generally safe with respect to risk of malignancy in the short term, the risk of recurrence in patients with RA with history of cancer or cancer risk factors remains unknown.

Author Contributions: Dr Suarez-Almazor 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.
Study concept and design: Lopez-Olivo, Martinez-Lopez, Suarez-Almazor.
Acquisition of data: Lopez-Olivo, Tayar, Martinez-Lopez, Pollono, Cueto, Gonzales-Crespo, Fulton.
Analysis and interpretation of data: Lopez-Olivo, Tayar, Martinez-Lopez, Gonzales-Crespo, Suarez-Almazor.
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Critical revision of the manuscript for important intellectual content: Lopez-Olivo, Tayar, Martinez-Lopez, Pollono, Cueto, Gonzales-Crespo, Fulton, Suarez-Almazor.
Statistical analysis: Lopez-Olivo, Martinez-Lopez.
Obtained funding: Cueto, Suarez-Almazor.
Administrative, technical, or material support: Martinez-Lopez, Pollono, Cueto, Fulton.
Study supervision: Lopez-Olivo, Tayar, Suarez-Almazor.
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