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Melanoma Risk in Patients Treated With Biologic Therapy for Common Inflammatory Diseases
A Systematic Review and Meta-analysis

Shamarke Esse, MRes; Kayleigh J. Mason, PhD; Adele C. Green, MBBS, PhD; Richard B. Warren, MBChB, PhD

IMPORTANCE Biologic therapies are widely prescribed immunomodulatory agents. There are concerns that compared with treatment with conventional systemic therapy, long-term biologic treatment for common immune-mediated inflammatory diseases, namely inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and psoriasis, may be associated with increased risk of melanoma.

OBJECTIVE To examine whether biologic treatment of IBD, RA, or psoriasis is associated with an increased risk of melanoma compared with conventional systemic therapy.

DATA SOURCES Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles published from January 1, 1995, to February 7, 2019, for eligible studies.

STUDY SELECTION Randomized clinical trials, cohort studies, and nested case-control studies quantifying the risk of melanoma in biologic-treated patients with IBD, RA, and psoriasis compared with patients treated with conventional systemic therapy were included.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted key study characteristics and outcomes. Study-specific risk estimates were pooled, and random- and fixed-effects model meta-analyses were conducted. Heterogeneity was assessed using the I^2 statistic. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines were followed.

MAIN OUTCOMES AND MEASURES The pooled relative risk (pRR) of melanoma in biologic-treated patients with IBD, RA, and psoriasis compared with biologic-naive patients treated with conventional systemic therapy.

RESULTS Seven cohort studies comprising 34 029 biologic-treated patients and 135 370 biologic-naive patients treated with conventional systemic therapy were eligible for inclusion. Biologic treatment was positively associated with melanoma in patients with IBD (pRR, 1.20; 95% CI, 0.60-2.40), RA (pRR, 1.20; 95% CI, 0.83-1.74), or psoriasis (hazard ratio, 1.57; 95% CI, 0.61-4.09) compared with those who received conventional systemic therapy, but the differences were not statistically significant. Adjustment for other risk factors was absent from most studies.

CONCLUSIONS AND RELEVANCE The findings suggest that clinically important increases in melanoma risk in patients treated with biologic therapy for common inflammatory diseases cannot be ruled out based on current evidence. However, further studies with large patient numbers that adjust for key risk factors are needed to resolve the issue of long-term safety of biologic therapy.

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Supplemental content

Author Affiliations: Division of Musculoskeletal and Dermatological Sciences, University of Manchester, Manchester, United Kingdom (Esse); Dermatology Centre, Manchester Academic Health Science Centre, NIHR Manchester Biomedical Research Centre, Salford Royal NHS Foundation Trust, University of Manchester, Manchester, United Kingdom (Esse, Mason, Green, Warren); QIMR Berghofer Medical Research Institute, Brisbane, New South Wales, Australia (Green); Cancer Research UK Manchester Institute, Faculty of Biology, Medicine and Health, University of Manchester, United Kingdom (Green).

Corresponding Author: Shamarke Esse, MRes, Division of Musculoskeletal and Dermatological Sciences, University of Manchester, Oxford Road, Room 1.725, Stopford Building, Manchester M13 9PT, United Kingdom (shamarke.esse@postgrad.manchester.ac.uk).

Crohn disease and ulcerative colitis, collectively known as inflammatory bowel disease (IBD); rheumatoid arthritis (RA); and psoriasis are immune-mediated inflammatory diseases with overlapping genetic susceptibility and several treatment modalities.[1,2] The inflammatory cytokine tumor necrosis factor (TNF) α has proved to be critical in the immunopathogenesis of these diseases, and inhibition of this cytokine has revolutionized treatment outcomes.[2,3] However, the standard paradigm of care for immune-mediated inflammatory diseases dictates that those requiring systemic therapy are initially treated with conventional systemic therapy, such as methotrexate. If such therapies are contraindicated or response is considered inadequate, treatment progresses to biologic therapy. Highly cost-effective biosimilar TNF inhibitors (TNFIs) are currently the first-line biologic for all 3 of these immune-mediated inflammatory diseases, although other biologic classes are also commonly used.[4-7]

Despite a large body of evidence establishing the short-term safety and efficacy of biologic therapy compared with conventional systemic therapy, there are concerns regarding the longer-term risk of cancer in patients treated with biologic therapy compared with conventional systemic therapy.[8-11] Melanoma is a highly immunogenic skin cancer and therefore of concern to patients treated with TNFIs because melanoma risk increases with suppression of the immune system and TNF-α plays an important role in the immune surveillance of tumors.[12,13]

A number of studies[14-19] in biologic-treated patients with IBD, RA, and psoriasis have reported an increased risk of melanoma, but these studies have typically used the general population as the comparator. To date, systematic reviews[20,21] specifically examining the risk of melanoma in biologic-treated patients compared with biologic-naive patients treated with conventional systemic therapy have been limited to RA. A meta-analysis[20] of studies of biologic-treated patients with RA found that treatment with TNFIs was not significantly associated with increased risk of melanoma compared with conventional systemic therapy (pooled relative risk [pRR], 1.4; 95% CI, 0.70-2.60), but the authors concluded that a clinically meaningful risk of melanoma could not be ruled out.

The risk of melanoma in patients with IBD and psoriasis treated with biologic therapy compared with patients treated with conventional systemic therapy is even less clear.[22,23] A meta-analysis[24] examining risk of melanoma in patients with IBD did not include any study comparing biologic-treated patients with IBD with biologic-naive patients with IBD. To our knowledge, the only systematic review[25] of any cancer in biologic-treated patients with psoriasis identified a single study examining the risk of melanoma compared with the general population.

Melanoma is a potentially aggressive cancer caused primarily by exposure to UV radiation (UVR) from natural (sunlight) or artificial (tanning bed) sources, with skin pigmentation being a key genetic risk factor.[26,27] There has been a marked increase in the incidence of melanoma in recent decades in many countries, including the US, UK, Norway, and Sweden.[28] Despite the implementation of skin cancer prevention programs, melanoma incidence rates are expected to continue increasing in these populations for the next few decades.[28] Therefore, identifying whether patients with common immune-mediated inflammatory disorders who are increasingly prescribed immunomodulatory agents are at further increased risk of developing melanoma is important. We systematically reviewed all relevant published studies to date and conducted meta-analyses to estimate melanoma risk in patients with IBD, RA, and psoriasis treated with biologic therapy compared with those treated with only conventional systemic therapy.

Key Points

Question Are patients with inflammatory bowel disease, rheumatoid arthritis, and psoriasis who are treated with biologic therapies at a higher risk of melanoma compared with those treated with conventional systemic therapy?

Findings In this systematic review and meta-analysis of 7 cohort studies comprising 34 029 biologic-treated and 135 370 biologic-naive, systemically treated patients, biologic-treated patients with inflammatory bowel disease, rheumatoid arthritis, and psoriasis had an increased risk of melanoma compared with those who received conventional systemic therapy, but the difference was not statistically significant.

Meaning The findings suggest that a clinically meaningful increase in melanoma risk cannot be ruled out; further studies adjusting for key risk factors are required.

Methods

Search Strategy and Eligibility Criteria

The Embase, MEDLINE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched for eligible studies published between January 1, 1995, and February 7, 2019 (eTable 1 in the Supplement). The details of the search strategy for Embase, MEDLINE, and CENTRAL are presented in eTable 2 in the Supplement. No geographic or language restrictions were imposed. The database search was supplemented with hand searching of the reference sections of retrieved articles. Randomized clinical trials, open-label extension trials, cohort studies, and nested case-control studies comparing the risk of melanoma in patients with IBD, RA, or psoriasis were identified. Studies in which patients were treated with biologic therapy for at least 12 months and were compared with biologic-naive patients with similar clinical and disease characteristics treated with conventional systemic therapy alone were eligible for inclusion. Study eligibility was independently assessed by 2 of us (S.E. and K.J.M.), who screened titles and abstracts of studies and then read the studies in full. Disagreements about eligibility were resolved by discussion with a third reviewer (R.B.W.). This systematic review and meta-analysis was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (eTable 3 in the Supplement).

Data Extraction and Quality Assessment

The following items were extracted from included studies: lead author and year of publication, study design, source population and baseline demographics, type(s) of biologic therapy, comparator therapy, treatment duration, follow-up period, outcomes, and quantitative estimates with 95% CIs. Selection, matching, and outcome were assessed for included cohort studies using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies[29] (eTable 4 and eTable 5 in the Supplement). Studies were assessed for adjustment for the following risk factors: age, sex, UVR exposure, concomitant or previous exposure to conventional systemic therapy, exposure to phototherapy with psoralen-UV-A (PUVA), and skin color (eTable 6 in the Supplement).

Statistical Analysis

The pRRs and 95% CIs were calculated for IBD and RA using the generic inverse variance approach. In studies providing multiple RR estimates, those adjusted for the greatest number of confounders were adopted. Statistical heterogeneity across the included studies was assessed using the Q statistic (χ^2 test), with a 2-sided significance level of $P < .05$, and quantified by the I^2 statistic. An I^2 statistic of 50% or greater was considered to represent significant heterogeneity. The random-effects model was adopted in anticipation of clinical heterogeneity. Prespecified sensitivity analyses were performed by excluding point estimates from the meta-analysis to ensure that overall risk estimates were not markedly affected by individual studies. In response to the large number of TNFI-treated patients identified in our literature search, a post hoc secondary analysis of melanoma risk in TNFI-treated patients with IBD and RA under a fixed-effects model was performed. Factors considered for subgroup analyses were mechanism of biologic therapy, treatment duration, and adjustment for risk factors. Publication bias was evaluated through visual inspection of a funnel plot and using the Begg and Egger tests in which $P \leq .05$ indicated significant publication bias. All analyses were conducted using Stata statistical software, version 14.1 (StataCorp).

Results

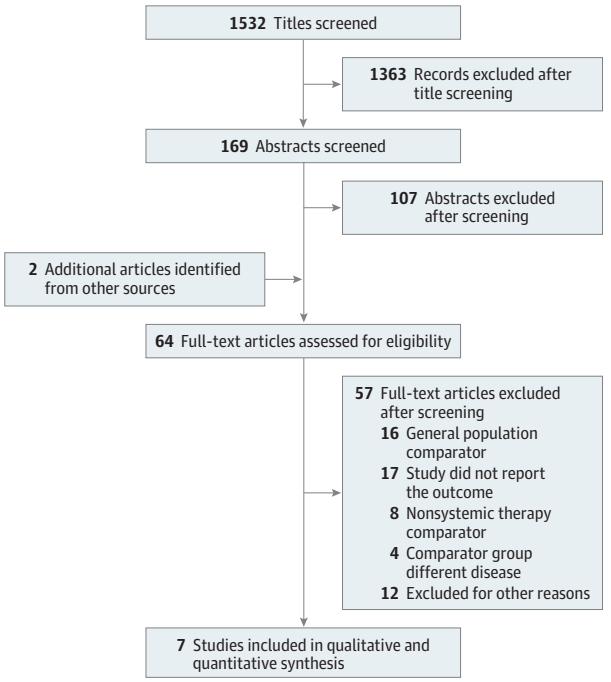
Search Results

We identified 1532 records after removing duplicates (**Figure 1**). After title screening, we removed 1363 records, with an additional 107 records excluded by abstract screening. The remaining 62 articles along with 2 additional articles identified by hand-searching were read in full and screened for eligibility. After 57 articles were excluded for ineligibility, 7 studies remained for analysis.

Characteristics of Included Studies

The 7 included studies were published between 2007 and 2019, and all were cohort studies conducted in the US (n = 3), Denmark (n = 2), Sweden (n = 1), and Australia (n = 1). Most studies (n = 5) used population-based registries, with 2 studies performed using health insurance databases.[30,31] Two studies were conducted with patients with IBD,[30,32] 4 with patients with RA,[33-36] and 1 with patients with psoriasis.[31] In total, 34 029 patients received biologic treatment and 135 370 biologic-naive patients received conventional systemic therapy. Mean patient follow-up duration ranged from 1.0 to 5.48 years, with study periods ranging from 1998 to 2015 (**Table**).

Figure 1. Flowchart for the Literature Search Results



Most included studies (n = 6) consisted of patients treated with TNFIs.[30,32-36] Five studies[30,32-35] pooled all patients treated with TNFIs, and 1 study[36] reported individual effect estimates for patients treated with the TNFIs adalimumab, etanercept, and infliximab. Asgari et al[31] pooled all patients treated with biologic therapy (97% treated with TNFIs). In addition to TNFI-treated patients, patients treated with abatacept (CD-28 inhibitor) and rituximab (CD-20 inhibitor) were also included in the study by Wadström et al.[35]

Adjustment for age and sex was performed in all included studies. Adjustment for previous or concomitant exposures to immunosuppressive therapies was performed in 1 study,[32] with adjustment for race/ethnicity (an indicator of skin color, a major risk factor for melanoma) performed in 1 study[31] (eTable 6 in the Supplement). Exposure to UVR was not reported or adjusted for in any of the included studies.

Risk of Melanoma

The pRR estimates for patients treated with biologic therapy compared with conventional systemic therapy were 1.20 (95% CI, 0.60-2.40) for patients with IBD and 1.20 (95% CI, 0.83-1.74) for patients with RA (**Figure 2** and eFigure 1 in the Supplement). Heterogeneity was not significant in the IBD (I^2 = 0%) and RA (I^2 = 34.9%) subgroups. There was no evidence of publication bias (Begg P = .87; Egger P = .16) (eFigure 2 in the Supplement).

Table. Summary of Evidence

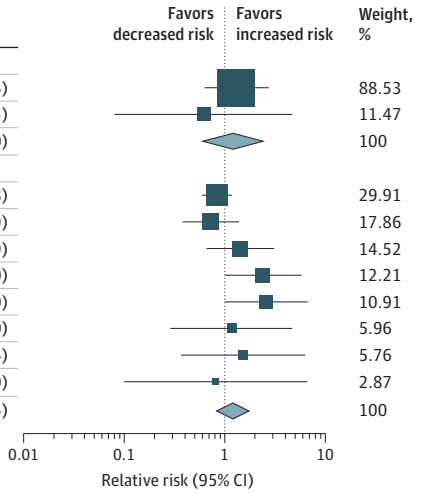
Source (study type)	Population source (study period)	Biologic cohort				Nonbiologic cohort				Estimate (95% CI)	Adjustment for confounders[a]
		Age, mean, y/female, %	Patients receiving therapy, No.	Treatment duration, mean	Cases, No.	Age, mean, y/female, %	Patients receiving therapy, No.	Treatment duration, mean	Cases, No.		
IBD											
Nyboe Andersen et al,[32] 2014 (cohort study)	The Danish National Patient Registry (1999-2012)	NR/56	TNFI: 4553	3.7 y	9	NR/55	IBD biologic naive: 51 593	NR	176	RR, 1.31 (0.63-2.74)	Disease duration; use of methotrexate, cyclosporine-cyclophosphamide, and azathioprine
McAuliffe et al,[30] 2015 (cohort study)	The HealthCore Integrated Research Database (2004-2011)	NR/49	TNFI: 3348	1.0 y	1	NR/49	IBD biologic naive: 29 472	NR		HR, 0.62 (0.08-4.75)	No additional adjustment performed
RA											
Dreyer et al,[33] 2013 (cohort study)	The Danish Registry for Biologic Therapies in Rheumatology (2000-2008)	54.3/73	TNFI: 3347	2.9 y	6	61.2/74	Nonbiologic DMARDs: 3812	NR	3	HR, 1.54 (0.37-6.34)	Calendar time
Staples et al,[34] 2019 (cohort study)	The Australian Rheumatology Association Database (2001-2012)	55.7/73.9	TNFI: 2451	10 120 person-years	12	62.4/70	Nonbiologic DMARDs: 574	2232 person-years	4	RR, 1.18 (0.29-4.70)	Calendar year, smoking status, methotrexate use, and prior malignant tumor
Wadström et al,[35] 2017 (cohort study)	The Swedish Rheumatology Quality of Care Register (2006-2015)	58/74	TNFI: 10 744	4.83 y	32	64/71	Conventional systemic DMARDs: 46 315	5.9 y	234	HR, 0.84 (0.60-1.18)	Start of treatment year, comorbidities, No. of hospitalizations, educational level, and days spent in inpatient care
		61/70	Abatacept: 2005	3.17 y	7					HR, 1.43 (0.66-3.09)	
		63/76	Rituximab: 3545	4.23 y	9					HR, 0.73 (0.38-1.39)	
Wolfe and Michaud,[36] 2007 (cohort study)	US National Data Bank for Rheumatic Diseases (1998-2005)	58.5/78	Infliximab: 790	2.9 y	11	58.5/78	Biologic naive: NR	NR	NR	OR, 2.60 (1.00-6.70)	Educational level, smoking history, baseline patient activity scale, and baseline prednisone use
			Etanercept: 754	2.7 y	9					OR, 2.40 (1.00-5.80)	
			Adalimumab: 207	1.2 y	1					OR, 0.80 (0.10-6.60)	
Psoriasis											
Asgari et al,[31] 2017 (cohort study)	Kaiser Permanente Northern California health insurance database (1998-2011)	47.6/47	Biologics: 2285	5.86 y	8	62.4/51	Nonbiologic systemic therapy: 3604	5.23 y	13	HR, 1.57 (0.61-4.09)	Race/ethnicity, presence of PsA; prior UV light therapy, BMI, and cigarette use

Abbreviations: BMI, body mass index; DMARDs, disease-modifying antirheumatic drugs; HR, hazard ratio; NR, not reported; IBD, inflammatory bowel disease; OR, odds ratio; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RR, relative risk; TNFI, tumor necrosis factor inhibitor.

[a] All studies were adjusted for age and sex.

Figure 2. Forest Plot of the Risk of Melanoma in Biologic-Treated Patients With Inflammatory Bowel Disease and Rheumatoid Arthritis Compared With Patients Treated With Conventional Systemic Therapy

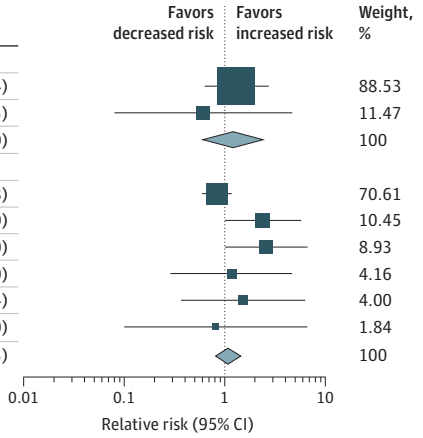
Study	Therapy	Relative risk (95% CI)	Weight, %
Inflammatory bowel disease			
Nyboe Andersen et al,[32] 2014	TNFI	1.31 (0.63-2.74)	88.53
McAuliffe et al,[30] 2015	TNFI	0.62 (0.08-4.75)	11.47
Subtotal I^2 = 0%, P = .50		1.20 (0.60-2.40)	100
Rheumatoid arthritis			
Wadström et al,[35] 2017	TNFI	0.84 (0.60-1.18)	29.91
Wadström et al,[35] 2017	Rituximab	0.73 (0.38-1.39)	17.86
Wadström et al,[35] 2017	Abatacept	1.43 (0.66-3.09)	14.52
Wolfe and Michaud,[36] 2007	Etanercept	2.40 (1.00-5.80)	12.21
Wolfe and Michaud,[36] 2007	Infliximab	2.60 (1.00-6.70)	10.91
Staples et al,[34] 2019	TNFI	1.18 (0.29-4.70)	5.96
Dreyer et al,[33] 2013	TNFI	1.54 (0.37-6.34)	5.76
Wolfe and Michaud,[36] 2007	Adalimumab	0.80 (0.10-6.60)	2.87
Subtotal I^2 = 34.9%, P = .15		1.20 (0.83-1.74)	100



Boxes indicate point estimates, with horizontal lines indicating 95% CIs. The size of the box is proportional to the weight of the study. Diamonds indicate pooled estimates with tips of the diamonds indicating 95% CIs. TNFI indicates tumor necrosis factor inhibitor.

Figure 3. Forest Plot of the Risk of Melanoma in Tumor Necrosis Factor Inhibitor (TNFI)–Treated Patients With Inflammatory Bowel Disease and Rheumatoid Arthritis Compared With Patients Treated With Conventional Systemic Therapy Under a Fixed-Effects Model

Study	Therapy	Relative risk (95% CI)	Weight, %
Inflammatory bowel disease			
Nyboe Andersen et al,[32] 2014	TNFI	1.31 (0.63-2.74)	88.53
McAuliffe et al,[30] 2015	TNFI	0.62 (0.08-4.75)	11.47
Subtotal I^2 = 0%, P = .50		1.20 (0.60-2.40)	100
Rheumatoid arthritis			
Wadström et al,[35] 2017	TNFI	0.84 (0.60-1.18)	70.61
Wolfe and Michaud,[36] 2007	Etanercept	2.40 (1.00-5.80)	10.45
Wolfe and Michaud,[36] 2007	Infliximab	2.60 (1.00-6.70)	8.93
Staples et al,[34] 2019	TNFI	1.18 (0.29-4.70)	4.16
Dreyer et al,[33] 2013	TNFI	1.54 (0.37-6.34)	4.00
Wolfe and Michaud,[36] 2007	Adalimumab	0.80 (0.10-6.60)	1.84
Subtotal I^2 = 43.8%, P = .11		1.08 (0.81-1.43)	100



Boxes indicate point estimates, with horizontal lines indicating 95% CIs. The size of the box is proportional to the weight of the study. Diamonds indicate pooled estimates with tips of the diamonds indicating 95% CIs.

The pRR estimate for patients with RA treated with only TNFI compared with those treated with conventional systemic therapy was 1.08 (95% CI, 0.81-1.43) (**Figure 3**). Compared with biologic-naive patients receiving conventional systemic therapy, the pRR of melanoma among the rituximab-treated patients with RA was 0.73 (95% CI, 0.38-1.39) and the pRR among the abatacept-treated patients with RA was 1.43 (95% CI, 0.66-3.09).[35] Sensitivity analysis that involved the exclusion of individual RA studies produced pooled risk estimates ranging from 0.91 (95% CI, 0.69-1.18), with the exclusion of the study by Wolfe and Michaud,[36] to 1.95 (95% CI, 1.16-3.30), with the exclusion of the study by Wadström et al.[35]

Quality Assessment

All included studies scored at least 7 of 9 and were deemed to be high quality; 5 of 7 studies scored 7 of 9, with the 2 remaining studies scoring 8 of 9 (eTable 5 in the Supplement). All these studies scored the maximum (4 of 4) for the selection domain and 2 of 3 for the outcome domain. The 2 highest-scoring studies scored the maximum of 2 of 2 for the matching domain because they adjusted for age, sex, and at least concomitant or previous exposure to immunosuppressive therapy or race/ethnicity.

Discussion

In this systematic review and meta-analysis, we did not find a statistically significant association between biologic exposure and development of melanoma in patients with IBD, RA, and psoriasis compared with patients receiving conventional systemic therapy. Our meta-analysis is the first, to our knowledge, to specifically examine the risk of melanoma in biologic-treated patients with IBD and psoriasis compared with their

biologic-naive counterparts receiving conventional systemic therapy. To date, the only other systematic review and meta-analysis[24] examining the risks of melanoma in IBD reported an increased risk of melanoma in patients with IBD independent of treatment with TNFIs. However, this finding was based on a subgroup analysis of 2 studies,[37,38] neither of which compared TNFI-treated patients with biologic-naive patients with IBD. The absence of a biologic-naive comparator group with IBD consisting of patients treated with systemic therapy in both studies leaves unanswered the question of whether any observed effect is attributable to the primary disease, treatment with systemic therapy, or both. Our study represents a more robust and clinically relevant analysis of the risk of melanoma in biologic-treated patients with IBD than the previous meta-analysis[24] because we restricted our inclusion criteria to studies that directly compared biologic-treated patients with IBD with biologic-naive patients with IBD.

The only published systematic review,[25] to our knowledge, that examined the risk of cancer in biologic-treated patients with psoriasis did not identify any published study that compared the risk of melanoma with that of biologic-naive patients treated with conventional systemic therapy for inclusion. Although we were unable to perform a meta-analysis for this subgroup, we included the only published study,[31] to our knowledge, comparing the risk of melanoma between biologic-treated patients and biologic-naive patients treated with conventional systemic therapy, suggesting no statistically significant increased risk of melanoma in biologic-treated patients.

Our study updates and extends another meta-analysis[20] of melanoma risk in biologic-treated patients with RA by including more recent reports from the Swedish[35] and Australian[34] registries. We also expanded the previous analysis[20] by including point estimates for rituximab and abatacept.[35] The results of our study correspond with those of the previous analysis, suggesting that treatment with biologics is not significantly associated with an increased risk of melanoma in patients with RA compared with biologic-naive patients treated with conventional systemic therapy.

Future Studies

Future population-based studies will need to account for the rapidly changing landscape of biologic treatment in IBD, RA, and psoriasis. The introduction of biologic therapies that target interleukins 6, 23, and 17 has expanded the available treatment options for patients initiating biologic therapy. Future studies should consider the various biological mechanisms of these therapies, their potential role in the development of melanoma, and how exposure to multiple classes of biologic therapies might affect a patient's risk of melanoma. To account for confounding by indication, studies should compare patients treated with TNFIs with patients treated with the newer biologics and those treated with more than 1 type of biologic.

Another development in the treatment of IBD, RA, and psoriasis is the introduction of TNFI biosimilars. Provision of biologic therapy varies globally, with health economic considerations often dictating access and uptake. Switching patients from reference TNFIs to biosimilars for cost-effectiveness has led to significant savings for health care practitioners in the UK, with similar savings projected for other European countries. This finding may lead to greater access for patients requiring these treatments, with possible earlier intervention in patients with IBD and psoriasis currently treated with only nonbiologic systemic therapy.[39-42]

Strengths and Limitations

The main strengths of our study included the use of a predefined protocol with strict inclusion and exclusion criteria. The systematic and comprehensive nature of our literature search of multiple databases, guided by our protocol, addressed a focused and clinically relevant research question with standardized data extraction and quality assessment to minimize errors.

The main limitation of our systematic review and meta-analysis was the small number of disease-specific studies that examined the risk of melanoma between biologic-treated patients and patients treated with conventional systemic therapy. Despite our extensive literature search, we identified only 2 studies on IBD and 1 study on psoriasis that were eligible for inclusion. The small number of studies eligible for inclusion meant that the pooled risk estimates were likely to be disproportionately affected by single studies. In our sensitivity analysis that accounted for the effects of singular studies, we found that the pooled risk estimate in the RA group increased from 1.20 (95% CI, 0.83-1.74) to 1.95 (95% CI, 1.16-3.30), suggesting a near 2-fold statistically significant increased risk of melanoma with the exclusion of the study by Wadström et al.[35] Any future update of our study through the inclusion of newly published studies may produce significantly different pooled risk estimates than those reported in our meta-analysis.

Another potential limitation of our study was the inclusion of studies performed using health insurance databases.[30,31] Unlike pharmacovigilance registries, health care insurance databases are primarily designed to collect health data for financial reimbursement and not to answer research questions related to treatment safety and effectiveness.[43] These studies had a greater risk of selection bias because patients were derived from databases that do not include uninsured patients or those with other health insurance policies. Health insurance database studies can also be prone to misclassifications of exposure because of treatment status being identified through prescriptions and the healthy user or adherer effect, in which patients who comply with treatment for a prolonged time are more likely to be healthy.[44]

A major weakness of the studies included in our analysis was the absence of adjustment for established risk factors for melanoma, such as UVR exposure and race/ethnicity. Significant differences in the cumulative exposure to UVR in the form of holiday sun exposure and prevalent tanning bed use or the number of patients from nonwhite racial/ethnic groups between the biologic-treated patients and biologic-naive patients treated with conventional systemic therapy could have led to an underestimation or overestimation of melanoma risk. Phototherapy with PUVA, formerly a common treatment for patients with psoriasis, is associated with an increased risk of melanoma.[45,46] Although the study by Asgari et al[31] report-

edly adjusted for previous phototherapy, it was not clear whether treatment with PUVA was included.

Treatment duration for conventional systemic therapy was poorly reported in the included studies (Table). Adjustment for differences in concomitant and historical treatment with conventional systemic therapy was absent from most of the included studies. Significant differences in duration (and therefore cumulative amount) of these immunosuppressive treatments between the biologic-treated patients and the patients treated with conventional systemic therapy could have biased our results. Moreover, given the generally long latency period between causal exposure and the development of melanoma, follow-up periods for biologic-treated patients in the included studies may not have been long enough and could have resulted in an underestimation of risk.

Conclusions

This study did not find a significant association between biologic exposure and development of melanoma compared with conventional systemic treatment. We advocate for more large, well-designed studies of this issue to be performed to help improve certainty. Prospective cohort studies using an active-comparator, new-user study design providing detailed information on treatment history, concomitant treatments, biologic and conventional systemic treatment duration, recreational and treatment-related UV exposure, skin color, and date of melanoma diagnosis are required to help improve certainty. These studies would also need to account for key risk factors and the latency period of melanoma.

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Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Esse, Green.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Esse.
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Conflict of Interest Disclosures: Dr Mason reported receiving personal fees from Janssen, LEO Pharma, Lilly, and Novartis outside the submitted work. Dr Warren reported receiving grants from AbbVie, Almirall, Amgen, Celgene, Janssen, Lilly, LEO Pharma, Novartis, and Pfizer during the conduct of the study and receiving personal fees from AbbVie, Almirall, Amgen, Arena, Avillion, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi, and UCB outside the submitted work. No other disclosures were reported.

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REFERENCES

1. David T, Ling SF, Barton A. Genetics of immune-mediated inflammatory diseases. *Clin Exp Immunol*. 2018;193(1):3-12. doi:10.1111/cei.13101

2. Beyaert R, Beaugerie L, Van Assche G, et al. Cancer risk in immune-mediated inflammatory diseases (IMID). *Mol Cancer*. 2013;12(1):98. doi:10.1186/1476-4598-12-98

3. Kuek A, Hazleman BL, Ostör AJK. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. *Postgrad Med J*. 2007;83(978):251-260. doi:10.1136/pgmj.2006.052688

4. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017;76(6):960-977. doi:10.1136/annrheumdis-2016-210715

5. Greb JE, Goldminz AM, Elder JT, et al. Psoriasis. *Nat Rev Dis Primers*. 2016;2(1):16082. doi:10.1038/nrdp.2016.82

6. Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet*. 2012;380(9853):1606-1619. doi:10.1016/S0140-6736(12)60150-0

7. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet*. 2012;380(9853):1590-1605. doi:10.1016/S0140-6736(12)60026-9

8. Murdaca G, Colombo BM, Cagnati P, Gulli R, Spanò F, Puppo F. Update upon efficacy and safety of TNF-α inhibitors. *Expert Opin Drug Saf*. 2012;11(1):1-5. doi:10.1517/14740338.2012.630388

9. Kamata M, Tada Y. Safety of biologics in psoriasis. *J Dermatol*. 2018;45(3):279-286. doi:10.1111/1346-8138.14096

10. Cohen BL, Sachar DB. Update on anti-tumor necrosis factor agents and other new drugs for inflammatory bowel disease. *BMJ*. 2017;357:j2505. doi:10.1136/bmj.j2505

11. Wilton KM, Matteson EL. Malignancy incidence, management, and prevention in patients with rheumatoid arthritis. *Rheumatol Ther*. 2017;4(2):333-347. doi:10.1007/s40744-017-0064-4

12. Crusz SM, Balkwill FR. Inflammation and cancer: advances and new agents. *Nat Rev Clin Oncol*. 2015;12(10):584-596. doi:10.1038/nrclinonc.2015.105

13. Passarelli A, Mannavola F, Stucci LS, Tucci M, Silvestris F. Immune system and melanoma biology: a balance between immunosurveillance and immune escape. *Oncotarget*. 2017;8(62):106132-106142. doi:10.18632/oncotarget.22190

14. Leonardi C, Papp K, Strober B, et al. Long-term safety of adalimumab in adult patients with plaque psoriasis. *Br J Dermatol*. 2019;180(1):e13-e13. doi:10.1111/bjd.17366

15. Papp KA, Griffiths CE, Gordon K, et al; PHOENIX 1 Investigators; PHOENIX 2 Investigators; ACCEPT Investigators. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. *Br J Dermatol*. 2013;168(4):844-854. doi:10.1111/bjd.12214

16. Buchbinder R, Van Doornum S, Staples M, Lassere M, March L. Malignancy risk in Australian rheumatoid arthritis patients treated with anti-tumour necrosis factor therapy: analysis of the Australian Rheumatology Association Database (ARAD) prospective cohort study. *BMC Musculoskelet Disord*. 2015;16(1):309. doi:10.1186/s12891-015-0772-2

17. Fleischmann RM, Tesser J, Schiff MH, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2006;65(8):1006-1012. doi:10.1136/ard.2005.048371

18. Lichtenstein GR, Feagan BG, Cohen RD, et al. Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT™ Registry. *Am J Gastroenterol*. 2014;109(2):212-223. doi:10.1038/ajg.2013.441

19. Pedersen N, Duricova D, Elkjaer M, Gamborg M, Munkholm P, Jess T. Risk of extra-intestinal cancer in inflammatory bowel disease: meta-analysis of population-based cohort studies. *Am J Gastroenterol*. 2010;105(7):1480-1487. doi:10.1038/ajg.2009.760

20. Olsen CM, Green AC. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: an updated meta-analysis. *Ann Rheum Dis*. 2018;77(8):e49. doi:10.1136/annrheumdis-2017-212205

21. Mariette X, Matucci-Cerinic M, Pavelka K, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. *Ann Rheum Dis*. 2011;70(11):1895-1904. doi:10.1136/ard.2010.149419

22. Annese V, Beaugerie L, Egan L, et al; ECCO. European evidence-based consensus: inflammatory bowel disease and malignancies. *J Crohns Colitis*. 2015;9(11):945-965. doi:10.1093/ecco-jcc/jjv141

23. Geller S, Xu H, Lebwohl M, Nardone B, Lacouture ME, Kheterpal M. Malignancy risk and recurrence with psoriasis and its treatments: a concise update. *Am J Clin Dermatol*. 2018;19(3):363-375. doi:10.1007/s40257-017-0337-2

24. Singh S, Nagpal SJ, Murad MH, et al. Inflammatory bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2014;12(2):210-218. doi:10.1016/j.cgh.2013.04.033

25. Peleva E, Exton LS, Kelley K, Kleyn CE, Mason KJ, Smith CH. Risk of cancer in patients with psoriasis on biological therapies: a systematic review. *Br J Dermatol*. 2018;178(1):103-113. doi:10.1111/bjd.15830

26. Leonardi GC, Falzone L, Salemi R, et al. Cutaneous melanoma: from pathogenesis to therapy [review]. *Int J Oncol*. 2018;52(4):1071-1080.

27. Duffy DL, Zhao ZZ, Sturm RA, Hayward NK, Martin NG, Montgomery GW. Multiple pigmentation gene polymorphisms account for a substantial proportion of risk of cutaneous malignant melanoma. *J Invest Dermatol*. 2010;130(2):520-528. doi:10.1038/jid.2009.258

28. Olsen CM, Green AC, Pandeya N, Whiteman DC. Trends in melanoma incidence rates in eight susceptible populations through 2015. *J Invest Dermatol*. 2019;139(6):1392-1395. doi:10.1016/j.jid.2018.12.006

29. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses coding manual [Internet]. Ottawa, Canada: The Ottawa Hospital Research Institute. Accessed June 1, 2019. http://www.ohri.ca/programs/clinical_epidemiology/nos_manual.pdf

30. McAuliffe ME, Lanes S, Leach T, et al. Occurrence of adverse events among patients with inflammatory bowel disease in the HealthCore Integrated Research Database. *Curr Med Res Opin*. 2015;31(9):1655-1664. doi:10.1185/03007995.2015.1065242

31. Asgari MM, Ray GT, Geier JL, Quesenberry CP. Malignancy rates in a large cohort of patients with systemically treated psoriasis in a managed care population. *J Am Acad Dermatol*. 2017;76(4):632-638. doi:10.1016/j.jaad.2016.10.006

32. Nyboe Andersen N, Pasternak B, Basit S, et al. Association between tumor necrosis factor-α antagonists and risk of cancer in patients with inflammatory bowel disease. *JAMA*. 2014;311(23):2406-2413. doi:10.1001/jama.2014.5613

33. Dreyer L, Mellemkjær L, Andersen AR, et al. Incidences of overall and site specific cancers in TNFα inhibitor treated patients with rheumatoid arthritis and other arthritides: a follow-up study from the DANBIO Registry. *Ann Rheum Dis*. 2013;72(1):79-82. doi:10.1136/annrheumdis-2012-201969

34. Staples MP, March L, Hill C, Lassere M, Buchbinder R. Malignancy risk in Australian rheumatoid arthritis patients treated with anti-tumour necrosis factor therapy: an update from the Australian Rheumatology Association Database (ARAD) prospective cohort study. *BMC Rheumatol*. 2019;3:1. doi:10.1186/s41927-018-0050-7

35. Wadström H, Frisell T, Askling J; Anti-Rheumatic Therapy in Sweden (ARTIS) Study Group. Malignant neoplasms in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors, tocilizumab, abatacept, or rituximab in clinical practice: a nationwide cohort study from Sweden. *JAMA Intern Med*. 2017;177(11):1605-1612. doi:10.1001/jamainternmed.2017.4332

36. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis Rheum*. 2007;56(9):2886-2895. doi:10.1002/art.22864

37. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology*. 2012;143(2):390-399.e1. doi:10.1053/j.gastro.2012.05.004

38. Peyrin-Biroulet L, Chevaux JB, Bouvier AM, Carrat F, Beaugerie L. Risk of melanoma in patients who receive thiopurines for inflammatory bowel disease is not increased. *Am J Gastroenterol*. 2012;107(9):1443-1444. doi:10.1038/ajg.2012.181

39. Aladul MI, Fitzpatrick RW, Chapman SR. The effect of new biosimilars in rheumatology and gastroenterology specialities on UK healthcare budgets: results of a budget impact analysis. *Res Social Adm Pharm*. 2019;15(3):310-317. doi:10.1016/j.sapharm.2018.05.009

40. Jha A, Upton A, Dunlop WC, Akehurst R. The budget impact of biosimilar infliximab (Remsima®) for the treatment of autoimmune diseases in five European countries. *Adv Ther*. 2015;32(8):742-756. doi:10.1007/s12325-015-0233-1

41. Barker J, Girolomoni G, Egeberg A, Goncalves J, Pieper B, Kang T. Anti-TNF biosimilars in psoriasis: from scientific evidence to real-world experience. *J Dermatolog Treat*. 2019:1-7. doi:10.1080/09546634.2019.1610553

42. Peyrin-Biroulet L, Danese S, Cummings F, et al. Anti-TNF biosimilars in Crohn's disease: a patient-centric interdisciplinary approach. *Expert Rev Gastroenterol Hepatol*. 2019;13(8):731-738. doi:10.1080/17474124.2019.1645595

43. Hyman J. The limitations of using insurance data for research. *J Am Dent Assoc*. 2015;146(5):283-285. doi:10.1016/j.adaj.2015.02.010

44. Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. *J Gen Intern Med*. 2011;26(5):546-550. doi:10.1007/s11606-010-1609-1

45. Stern RS; PUVA Follow up Study. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol*. 2001;44(5):755-761. doi:10.1067/mjd.2001.114576

46. Archier E, Devaux S, Castela E, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol*. 2012;26(suppl 3):22-31. doi:10.1111/j.1468-3083.2012.04520.x