Melanoma risk during immunomodulating treatment

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Immunosuppressive therapy is standard for the treatment of inflammatory diseases and for minimizing rejection in transplant patients. However, immunosuppressant drugs are associated with an increased risk of certain cancers. In particular, melanoma is an immunogenic tumor and as such, is strongly influenced by the immune system. We performed this literature review to summarize the effects of commonly used immunomodulating agents on melanoma development, recurrence and progression. We outline the mechanism of action of each drug and discuss the available evidence on its influence on melanoma. Based on existing literature, we recommend avoiding the following agents in patients with a history of invasive melanoma: cyclosporine, sirolimus, natalizumab, IL-6 inhibitors, cyclophosphamide, methotrexate and the tumor necrosis factor-alpha inhibitors infliximab and etanercept. If there are no viable alternative agents, we recommend for these patients to see a dermatologist every 6 months for a thorough skin examination. *Melanoma Res* 32: 411–418

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Introduction

The immune system is a major mechanism for the prevention of malignancies. The term 'cancer immunoediting' describes this in three main processes: elimination, equilibrium and escape. The key feature of the elimination process is the detection and elimination of nascent tumor cells by the innate immune system. If elimination is unsuccessful, tumor cells with increasing ability to resist immune attack are selected for in the equilibrium phase. In the escape process, tumor cells escape this control through genetic or epigenetic changes resulting in clinically observable malignant disease [1].

Melanoma is a prime example of an immunogenic tumor. The assertion is made from these observations: (1) primary melanomas often exhibit strong lymphocytic infiltration inducing partial or complete regression; (2) development of vitiligo is a marker of better prognosis in melanoma patients[2] and (3) immunotherapies have shown remarkable long-term results [3,4].

Due to this close connection between the immune system and melanoma, we can expect that immunosuppressive or immunomodulating drugs affect this balance. This review is intended to summarize the available evidence about the effects of immuno-therapeutics on melanoma development, disease recurrence and progression, and to be used as a tool for determining whether long-term dermatological follow-up is needed. We consider long-term epidemiologic data, in particular meta-analyses, to be the gold standard for assessing the risk related to certain immunoactive agents. Secondary, especially for drugs that have been introduced more recently, we also consider the mechanism of action important for the evaluation of the potential impact on melanoma.

Melanoma development in immunosupressed patients

In organ transplant recipients (OTRs), there is an increased risk for nonmelanoma skin cancers [5], but it remains controversial whether there is an increased risk of melanoma. While some large population studies did not find an increased risk for melanoma in immunosuppressed patients, others show a 2.1–8-fold higher incidence than in the general population [6]. These studies have not attributed the increased risk of melanoma to specific immunosuppressive drugs, which is a particular challenge given that immunosuppression often involves a multi-drug regimen.

Other common conditions that require immunomodulatory treatment include rheumatoid arthritis (RA), psoriasis and inflammatory bowel disease (IBD). A meta-analysis of malignancies in patients with RA found an increased risk of melanoma with an increased standardized incidence ratio (SIR) of 1.23 [95% confidence interval (CI), 1.01–1.49] but noted that study results were mixed [7]. Studies examining melanoma risk in patients with psoriasis or IBD are also conflicting [8,9].

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Table 1 Summary of melanoma risk association with common immunomodulatory drugs

Drug class	Drug name	Mechanism	Association with melanoma	Highest level of evidence	Recommendation	Ref.
Calcineurin inhibitor	Cyclosporin	Inhibit IL-2 which in turn inhibits T-cell replication	Yes	Retrospective cohort	Avoid[a]	[10]
	Tacrolimus		No	Retrospective cohort	No restrictions	[11]
mTOR inhibitor	Sirolimus	Binds FKBP-12 to form complex which inhibits mTOR and T-cell proliferation	Yes	Retrospective cohort	Avoid[a]	[10]
	Temsirolimus		No	Not reported	No restrictions	
	Evorolimus		No	Not reported	No restrictions	
Adhesion molecule inhibitor	Natalizumab	Binds to α4β1-integrin on WBCs, limiting migration	Yes	Review of safety data	Avoid[a]	[12]
IL-12 and IL-23 inhibitor	Ustekinumab	Binds to both IL-12 and IL-23, preventing them from binding receptors	No	Review of safety data	No restrictions	[13,14]
Antimetabolite	Mycophenolate mofetil	Pro-drug of mycophenolic acid, which inhibits purine synthesis	No	Retrospective cohort	No restrictions	[15]
Glucocorticoids	Multiple	Inhibitory effects on immune response through anti-inflammation	No	Case-control	No restrictions	[16–18]
Antimetabolite	Azathioprine	Inhibits purine metabolism and nucleic acid synthesis	No	Meta-analysis	No restrictions	[19]
Antimetabolite	Methotrexate	Folate antimetabolite that inhibits purine synthesis	Inconclusive	Meta-analysis	Avoid[a]	[20–22]
TNF-alpha inhibitors	Multiple	Blocks activity of TNF-alpha, which suppresses immune system	Inconclusive	Meta-analysis	Avoid infliximab and etanercept[a]	[23–28]
Alkylating agent	Cyclophosphamide	Crosslinks DNA and prevents cell division	Inconclusive	Retrospective cohort	Avoid[a]	[29]
IL-6 inhibitor	Tocilizumab	Binds IL-6R which inhibits T-cell proliferation	Inconclusive	Review of safety data	Avoid[a]	[23]

mTOR, mammalian target of rapamycin; TNF, tumor necrosis factor.
[a]Avoid in patients with any history of invasive melanoma. If there is no equivalent alternative therapy, patients should be scheduled for dermatological follow-up every 6 months.

Below, we discuss 11 common classes of immunomodulatory drugs (Table 1). We present the mechanism of action of each as well as any large studies (Table 2) and case reports. These studies were found by searching *PubMed* with the keywords 'melanoma and (drug name)' from the years 1990 to 2020. Variations of the drug name, including abbreviations or the class of medication, were also searched for when appropriate. Meta-analyses, cohort studies, case-control studies and case reports were examined if they were related to the secondary development of melanoma after the use of the agent. The degree of evidence is noted. Higher degrees of evidence include meta-analyses whereas lower degrees of evidence include case reports.

Increased melanoma risk

Calcineurin inhibitors: cyclosporine and tacrolimus

Cyclosporine and tacrolimus, both calcineurin inhibitors, inhibit the production of interleukin-2 (IL-2) which decreases T-cell-mediated immune responses. Increased production of transforming growth factor beta-1 also contributes to immunosuppression [34–38]. A retrospective case-control study found that among renal transplant recipients, the use of cyclosporine was associated with a 1.93 (95% CI, 1.24–2.99; $P = 0.004$) hazard ratio of developing melanoma compared to patients who did not use cyclosporine [10]. Additionally, a number of case reports describe patients who developed melanoma after being treated with cyclosporine monotherapy [39–41]. A 2012 review [42] of 60 studies found very few cases of melanoma in patients treated with cyclosporine but did not provide any statistical analysis. In a postmarketing surveillance study [43], only one case of melanoma was reported in more than 10 000 patients treated with cyclosporine. There are no studies reporting an increased risk of melanoma in patients systemically treated with tacrolimus. One retrospective cohort study [11] did not find any correlation between the use of topical tacrolimus and the development of melanoma. One case report [44] described a pediatric patient with vitiligo who developed melanoma after a 4-week course of tacrolimus ointment of 0.1%.

Mammalian target of rapamycin (mTOR) inhibitors: sirolimus, temsirolimus and everolimus

The mammalian target of rapamycin (mTOR) inhibitors (sirolimus, temsirolimus and everolimus) halt the progression from the G1 to S phase of the cell cycle, suppressing T-cell proliferation. However, through a similar mechanism, mTOR inhibitors also have antioncogenic effects [45,46]. Some studies [47,48] suggest that switching from calcineurin inhibitors to sirolimus has an antitumoral effect among kidney-transplant recipients with previous squamous-cell carcinoma. However, one retrospective case-control study found that among renal transplant patients, the use of sirolimus was associated with a hazard ratio of 1.54 (95% CI, 1.22–1.94; $P < 0.001$)

Table 2 Summary of important studies

Studies	Population source (study period)	Drug	Indication for drug	Type	n/N	c/C	Effect size (95% CI)	*P* value
Ascha *et al.* 2017 [10]	United States Renal Data System (2004–2012)	Cyclosporine	Renal transplant	Retrospective cohort	3341/ 101 833	24/464	HR, 1.93 (1.24–2.99)	0.004
Ascha *et al.* 2017 [10]	United States Renal Data System (2004–2012)	Tacrolimus	Renal transplant	Retrospective cohort	92 477/ 12 697	411/77	HR, 0.94 (0.72–1.24)	0.68
Hui *et al.* 2009 [11]	Kaiser Permanente Northern and Southern California (2001–2004)	Tacrolimus	Atopic dermatitis	Retrospective cohort	15 966/ 914 382	4/734	HR, 0.32 (0.12–0.84)	0.021
Ascha *et al.* 2017 [10]	United States Renal Data System (2004–2012)	Sirolimus	Renal transplant	Retrospective cohort study	13 973/ 91 237	109/379	HR, 1.54 (95% CI: 1.22–1.94)	<0.001
Kelm *et al.* 2019 [12]	FDA Adverse Event Reporting System (2004–2014)	Natalizumab	Multiple sclerosis	Pharmaco-vigilance study	NR/NR	205/NR	PRR 2.42 (2.10–2.8)	NR
Sørenson *et al.* 2004 [14]	North Jutland Prescription Database and the Danish Cancer Registry (1989–1996)	Glucocorticoids (multiple)	Any indication	Retrospective single cohort	59 043/ NA[a]	105/NA[a]	SIR, 1.30 (1.06–1.58)	0.04
Jensen *et al.* 2009 [30]	North Jutland Prescription Database and the Danish Cancer Registry (1989–2003)	Glucocorticoids (multiple)	Any indication	Case-control	163/710	983/4406	IRR, 1.15 (0.94–1.41)	NR
Landi *et al.* 2001 [31]	Maurizio Bufalini Hospital, Cesena, Italy	Glucocorticoids (multiple)	Any indication	Case-control	25/44	183/179	OR, 0.39, (0.20–0.74)	0.004
Huang *et al.* 2019 [29]	NA	Azathioprine	Inflammatory bowel disease	Meta-analysis, 13 studies	NA	NA	RR, 1.22, (0.90–1.65)	0.206
Buchbinder *et al.* 2008 [32]	Melbourne, Australia and Victorian State Cancer Registry	Methotrexate	Rheumatoid arthritis	Retrospective single cohort	458/NA[a]	7/NA[a]	SIR, 3.0 (1.2–6.2)	NR
Polesie *et al.* 2017 [15]	Swedish National Board of Health and Welfare (2005–2014)	Methotrexate	Rheumatoid arthritis	Retrospective cohort	101 966/ 5050 909	591/2506	HR, 1.17 (1.08–1.26)	0.0006
Pouplard *et al.* 2013 [16]	NA	Methotrexate	Rheumatoid arthritis	Meta-analysis, 6 studies	NA	NA	SIR, 1.07, (0.85–1.35)	0.58
Mariette *et al.* 2011 [33]	NA	TNFa inhibitor (multiple)	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	Meta-analysis, 2 studies	NA	NA	OR, 1.79 (0.92–2.67)	NR
Esse *et al.* 2020 [20]	NA	TNFa inhibitor (multiple)	Rheumatoid arthritis (RA), inflammatory bowel disease (IBD)	Meta-analysis, 4 studies for RA, 2 studies for IBD	NA	NA	RA RR, 1.08 (0.81–1.43); IBD RR, 1.20 (0.60–2.40)	NR
Olsen *et al.* 2018 [21]	NA	TNFa inhibitor (multiple)	Rheumatoid arthritis	Meta-analysis, 7 studies	NA	NA	SIR, 1.7 (1.2–2.3)	NR
Wolfe *et al.* 2007 [22]	US National Data Bank for Rheumatic Diseases (1998–2005)	TNFa inhibitor (multiple)	Rheumatoid arthritis	Retrospective single cohort	Infliximab 2587/ NA[a]; Etanercept 988/ NA[a]	Infliximab 11/ NA[a]; Etanercept 9/ NA[a]	Infliximab OR, 2.6 (1.0–6.7); Etanercept OR, 2.4 (1.0–5.8)	0.056, 0.054
Farschou *et al.* 2008 [27]	Danish Cancer Registry (1973–2003)	Cyclophosphamide	Wegner's granulomatosis	Retrospective single cohort	293/NA[a]	1/NA[a]	SIR, 1.7 (0.0–9.2)	NR

c, melanoma cases among drug cohort; C, melanoma cases among comparator; CI, confidence interval; FDA, Food and Drug Administration; HR, hazard ratio; IRR, incidence rate ratio; n. drug cohort; N, comparator cohort; NR, not reported; NA, not applicable; SIR, standardized incidence ratio; TNF, tumor necrosis factor.
[a]comparator is general population.

of developing melanoma compared to those who did not use sirolimus [10]. No association between either temsirolimus or everolimus and skin cancers has been noted, although both have been tried unsuccessfully as a treatment for melanoma [49–51].

Natalizumab

Natalizumab is a mAb against the alpha-4 subunit of integrin molecules, blocking leukocyte adhesion and transmigration. Several case reports describe patients who developed melanoma during therapy with natalizumab [52–55]. Importantly, a study examining the Food and Drug Administration (FDA) Adverse Events Reporting System across 10 years found 205 melanoma cases after natalizumab therapy for multiple sclerosis, which corresponded to a proportional reporting ratio of 2.42 (95% CI, 2.10–2.8) [12]. Patients treated with natalizumab also appear to be diagnosed with melanoma at a younger median age of 45 years [12]. This suggests that natalizumab exposure could be associated with the development of melanoma.

No increased melanoma risk

Interleukin-12 and Interleukin-23 inhibitors

IL-12 is involved in the induction of the innate immunity, promoting a Th1 response, and eliminating cancer cells [56]. Animal models demonstrate that IL-12 deficiency is associated with a higher risk of skin tumors [57]. On the other hand, IL-23 is associated with a Th17 response and has pro-tumorigenic effects of decreasing CD8+ T-cell infiltration and increasing angiogenesis [58,59]. Ustekinumab targets the common p40 subunit of IL-12 and IL-23, preventing receptor binding [60]. Clinical trials with ustekinumab for multiple indications have not identified an increased risk of malignancy [23,61] compared to placebo or general population and our search revealed only one case report of a patient developing melanoma during ustekinumab treatment [62].

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a pro-drug of mycophenolic acid, which inhibits inosine monophosphate dehydrogenase, a key enzyme in the de novo guanosine nucleotide synthesis. MMF affects B- and T-lymphocytes to a greater extent than cells of the innate immune system [63]. There are no studies that directly and reliably suggest that MMF can increase melanoma risk. A few studies describe the incidence of melanoma in organ transplant patients treated with various immunosuppressive regimens that include MMF, but there are no odds ratios (OR) reported or comparisons to controls [64–66]. A large retrospective study [13] found no evidence that patients treated with MMF have an increased risk of malignancies compared to patients treated with non-MMF-based immunosuppression regimens. Moreover, our literature search did not reveal reports of patients who developed melanoma during MMF monotherapy.

Glucocorticoids

Glucocorticoids are widely used for the treatment of many inflammatory, allergic, immunologic and malignant disorders. They inhibit a broad range of immune responses, including the innate and the adaptive immune system. One group examined a large retrospective cohort of Danish patients from 1989 to 1996 and found an increased risk of melanoma in patients systemically treated with a variety of glucocorticoids for any indication, with a SIR of 1.30 (95% CI, 1.06–1.58) [14]. Years later, the same group used an expanded cohort of Danish patients from 1989 to 2003, this time with matched controls, and found that there was no increased melanoma incidence rate ratio (IRR) among those patients (IRR = 1.15; 95% CI, 0.94–1.41) [30]. In a smaller case-control study of risk factors for cutaneous melanoma, authors [31] showed a protective effect of glucocorticoids (OR = 0.39; 95% CI, 0.2–0.74). However, this cohort included topically administered glucocorticoids rendering these conclusions incomparable to the previous studies.

Azathioprine

Azathioprine, and its active compound 6-mercaptopurine is an antimetabolite which antagonizes purine metabolism and inhibits the synthesis of DNA and RNA, resulting in decreased numbers of circulating B- and T-lymphocytes. A meta-analysis of patients treated with thiopurines for IBD found that there was no statistically significantly increased melanoma risk (RR = 1.22; 95% CI, 0.90–1.65; $P = 0.206$, 13 studies) [29]. However, there is an increase in excess nonmelanoma skin cancer risk (RR = 1.88; 95% CI, 1.48–2.38; $P < 0.001$, 13 studies) [29].

Inconclusive melanoma risk

Methotrexate

Methotrexate is a folate antimetabolite that binds to dihydrofolate reductase and thymidylate synthetase, resulting in decreased reduced folates, purines and pyrimidines. Several case reports discuss patients developing melanoma in the setting of long-term methotrexate therapy for RA [67–69]. One retrospective study of patients with RAtreated with methotrexate [32] found a threefold increased risk of developing melanoma compared to the general population (SIR = 3.0; 95% CI, 1.2–6.2). A retrospective study in Sweden of over 100 000 patients dispensed methotrexate compared to five times the number of matched controls found a small but statistically significant increase in the 5-year risk of melanoma in patients treated with methotrexate (0.48%; 95% CI, 0.43–0.53%) compared to the methotrexate-unexposed group (0.41%; 95% CI, 0.39–0.43); $P < 0.001$ [15]. However, a

meta-analysis of six studies of patients on methotrexate for psoriasis showed no significant increase in melanoma risk (SIR = 1.07; 95% CI, 0.85–1.35) [16]. Given conflicting evidence of large studies and a meta-analysis for varying indications of methotrexate, we cannot draw a definitive conclusion and recommend avoiding methotrexate in patients with a history of invasive melanoma.

Tumor necrosis factor-alpha inhibitors

Inhibitors of tumor necrosis factor-alpha (TNFi) are biologics which block the cytokine's pro-inflammatory effects. TNF-alpha plays a role in regulating the anti-tumor immune response [17,18]. Five TNFi are currently approved by the FDA: etanercept, infliximab, adalimumab, certolizumab pegol and golimumab. Most recent meta-analyses [20,33,70,71] conducted in patients treated with TNFi did not reveal any evidence for increased overall cancer risk. However, one meta-analysis of patients with RA treated with TNFi found a statistically significant increase in melanoma risk (1.7; 95% CI, 1.2–2.3; 7 studies) [21]. An observational study assessed melanoma risk by biologic drugs and found a trend of increased melanoma risk in patients treated with infliximab (OR = 2.6; 95% CI, 1.0–6.7; $P = 0.056$) and etanercept (OR = 2.4; 95% CI, 1.0–5.8; $P = 0.054$), but not in patients treated with adalimumab [22]. Some published case reports [24,25,72,73] describe patients who developed melanoma during the treatment with TNFi. Given a large number of conflicting studies and meta-analyses, we cannot draw a conclusion on the association between melanoma and TNFi. However, we recommend avoiding the TNFi infliximab and etanercept in patients with a history of invasive melanoma given the significant findings above.

Cyclophosphamide

Cyclophosphamide is an alkylating chemotherapeutic and immunosuppressive agent whose metabolite crosslinks DNA to interfere with DNA synthesis most often used to treat lymphoma. Some studies [26,27] suggest an increased neoplastic risk in patients treated with cyclophosphamide, particularly of urinary bladder cancer and acute myeloid leukemia. However, a conclusion could not be drawn regarding the risk of melanoma in patients treated with cyclophosphamide due to an insufficient number of cases. An observational cohort study [27] of 293 patients affected by Granulomatosis with polyangiitis and treated with cyclophosphamide revealed a SIR of 1.7 for melanoma compared to the general population; however, this did not reach statistical significance (95% CI, 0.0–9.2). Given a lack of data, we cannot make an assessment on melanoma risk.

Interleukin-6 inhibitors

IL-6 has functions that vary from reducing T-cell apoptosis to promoting tumorigenesis [28]. Tocilizumab is an IL-6 receptor antagonist used for the treatment of RA and systemic juvenile idiopathic arthritis. It is also being tested in clinical trials in combination with ipilimumab and nivolumab for advanced melanoma [74]. There are case reports that describe patients who developed melanoma during treatment with tocilizumab [75,76]. Larger studies and reviews of safety data suggest that there is no increased risk for malignancies compared to patients treated with synthetic disease-modifying antirheumatic drugs or the general population. However, specifically for melanoma, there were not enough cases for analysis [19,71,77]. Given a lack of data, we cannot make an assessment on melanoma risk.

The following immunomodulating agents have been found to be associated with an increased risk of melanoma or to have an inconclusive association with melanoma: cyclosporine, sirolimus, natalizumab, IL-6 inhibitors, cyclophosphamide, methotrexate and the TNF-alpha inhibitors infliximab and etanercept. In patients with the highest risk of developing melanoma, those with a history of invasive melanoma [78], we recommend these agents as second-line therapy and we suggest prioritizing a different agent if possible. Many of these therapies are used for life-threatening diseases including psoriatic arthritis, Sjogren's syndrome, inflammatory bowel disease and multiple sclerosis, and the association with melanoma, though significant, is small, so risks and benefits must be weighed proportionately. Thus, if there are no equal alternative agents, we recommend dermatologic follow-up every 6 months while taking the medication.

Risk of disease progression or recurrence in melanoma patients

Generally, patients with a diagnosis of early melanoma are considered cured and discharged from close follow-up after 5–10 years. However, up to 6.9% of melanoma patients experience recurrence even 10 years after initial diagnosis [79,80]. This event is defined as 'late recurrence' and could be explained by 'tumor dormancy': cancer cells persist below the threshold of diagnostic detection for months to decades. Given the important role of the immune system in containing malignancies, there is concern that immunosuppression can increase the risk of melanoma progression or recurrence.

A number of retrospective studies analyzed the risk of disease progression or recurrence after transplantation in patients with a history of melanoma. One retrospective study reported a 19% rate of recurrence (6/31 patients) after solid organ transplantation in patients with a history of melanoma [81]. However, the largest of the studies investigating this [82] analyzed 59 patients with a history of melanoma before transplantation and found no evidence of an increased risk of recurrence or disease progression compared to historical controls. Additional studies reveal similar findings that there is no increased

risk of recurrence or disease progression and suggest that a history of melanoma should not be a contraindication to transplantation [6,83,84].

The literature on the role of immunosuppressive drugs used in melanoma patients for other indications is limited to case reports. Lazarus *et al*. [85] reported a case of a local melanoma relapse in a patient treated with a one-time dose of intralesional glucocorticoid for a keloid in the surgical site of melanoma excision. Fulchiero *et al*. [86] described two patients who developed disease progression during TNFi treatment. The first developed melanoma lymph node metastasis while on adalimumab therapy for 6 months, 8 years after an initial stage IA diagnosis. The second developed regionally metastatic melanoma after 4 weeks of twice-weekly injections of etanercept for refractory psoriasis, after an initial diagnosis of stage IB melanoma 6 years prior.

Therefore, we recommend avoidance of agents associated with an increased melanoma risk or inconclusive risk in patients with any history of invasive melanoma, and dermatologic follow-up every 6 months if there are no available alternative therapies.

Melanoma prognosis during immunosuppressant treatment

The specific survival of patients who develop melanoma after organ transplantation might be decreased, especially for those patients with thicker primary tumors (>1.51 mm Breslow thickness or Clark III/IV) [82]. A study comparing melanoma survival rates between posttransplant patients and matched American Joint Committee on Cancer (AJCC) database controls with thin melanomas (T1 and T2, <2 mm) show no significant differences in survival [83]. However, transplant patients with thick melanomas (T3 and T4, >2 mm) observe a worse survival compared to AJCC control patients with thick melanomas (HR = 11.49; 95% CI, 3.59–36.82) [83].

Frankenthaler *et al*. [87] performed a case-control study to compare the prognosis of 19 patients with melanoma and concomitant immunosuppressive treatment (four OTRs and 15 immune-mediated disorders) to matched-control patients with melanoma receiving no immunologic treatment. They reported an equal relapse-free survival, but a worse overall survival in patients with concomitant immunosuppressive treatment. Although the reasons for decreased survival in these patients are incompletely understood, there may be a greater imperative to identify melanoma lesions early in patients on immunosuppressive treatment.

Conclusion

Limitations of this review include a limited selection of large studies with controls for certain drugs. Additionally, this study may not include all relevant literature, especially those not indexed in *PubMed*. Finally, some studies are for drugs for a specific indication, which may not be externally valid for the same drug for other indications. However, we erred on the side of caution by assuming generalizability when interpreting the data.

The association between immunomodulatory therapies and melanoma is of particular interest due to the nature of melanoma as an immunogenic tumor. There appears to be epidemiologic evidence that some immunosuppressive drugs, including cyclosporine, natalizumab and sirolimus are associated with melanoma. Additional agents such as IL-6 inhibitors, cyclophosphamide, methotrexate and the TNF-alpha inhibitors infliximab and etanercept either did not have sufficient data or had conflicting data regarding melanoma risk. Therefore, we recommend all patients with a history of invasive melanoma to avoid these agents due to their baseline high risk of melanoma. If there are no equivalent alternative therapies, these patients should receive dermatological follow-up every 6 months.

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Conflicts of interest

There are no conflicts of interests.

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