Incidence of Skin Cancer in Patients With Chronic Inflammatory Cutaneous Diseases on Targeted Therapies: A Systematic Review and Meta-Analysis of Observational Studies

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Cancer is one of the several comorbidities that have been linked with chronic cutaneous inflammatory diseases namely psoriasis/psoriatic arthritis and hidradenitis suppurativa. Although the chronic inflammatory state, typical of the diseases, may induce pro-tumorigenic effects, the debate whether or not the drugs currently used in clinical practice do in fact increase a patient’s risk of malignancy remains largely unsolved. The therapeutic armamentarium has been greatly enhanced at least in the last two decades with the advent of biologics, a heterogeneous group of laboratory-engineered agents with more in the pipeline, and other targeted small molecules. Among the organ systems, skin results as one of the most commonly affected, non-melanoma skin cancers being the main drug-induced manifestations as side effect in course of these treatments. The objective of the study is to systematically review the cutaneous malignancy risk of the newer therapies through an overview of meta-analyses and observational studies on the topic.

Keywords: skin cancer, non-melanoma skin cancer, melanoma, biologics, psoriasis

INTRODUCTION

Psoriasis, psoriatic arthritis and hidradenitis suppurativa are three common inflammatory and immune-mediated skin diseases characterized by increased levels of pro-inflammatory cytokines and chemokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-17 and IL-23 (1–7). Chemical inflammatory mediators involved in the pathogenesis of these diseases may increase the
risk of malignancies through the induction of pro-cancerous mutations, adaptive responses, resistance to apoptosis and environmental changes such as the stimulation of angiogenesis (8, 9). A number of observational studies suggested that patients affected by these diseases are at increased risk of developing cancer (10–13). In particular, increased rates of cancer, especially keratinocyte skin cancer and lymphomas were reported in patients with psoriasis or psoriatic arthritis (14). A significantly increased risk of overall cancer was observed also among patients affected by hidradenitis suppurativa in a recently published population-based cohort study (15).

The recent marketing of systemic biological (i.e. the TNF-α inhibitors etanercept, infliximab and adalimumab, the anti-IL-12/23 ustekinumab, the IL-17/IL-17 receptor antagonists secukinumab, ixekizumab and brodalumab and the anti-IL-23 agents tildrakizumab, guselkumab and risankizumab) and chemically synthetized drugs (e.g. apremilast and tofacitinib) as targeted therapies has improved the management of these diseases (16–18). However, since these drugs target molecules that may be relevant to cancer immunosurveillance mechanisms, some concerns were raised about their association with an increased risk of cancer occurrence (19–23). A recent meta-analysis of randomized clinical trials (RCTs) and open-label extension (OLE) studies reported that TNF inhibitors are associated with an increased risk of non-melanoma skin cancers (NMSC) in people with psoriasis. However, the authors of this study found that no real-world evidence was available and acknowledged the significant limitations associated with the study design of the articles included, that make it difficult to extrapolate to real-world practice (24). Evidence on the risk of skin cancer in patients with chronic inflammatory cutaneous diseases on targeted therapies is still sparse controversial. Therefore, the aim of this systematic review and meta-analysis was to assess the risk of cutaneous malignancies in patients with psoriasis, psoriatic arthritis or hidradenitis suppurativa treated with targeted therapies.

METHODS

Search Strategy and Study Selection Criteria

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, following an a priori-established protocol registered on the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020212137). The completed PRISMA checklist is provided in Supplementary Figure 1. Two authors (SC and FC) independently searched the bibliographic databases PubMed and EMBASE for literature related to the risk of skin cancer in patients affected by inflammatory cutaneous diseases and treated with targeted therapies. Literature was searched from databases inception until 15th September 2020. The search strategy concerned terms related to inflammatory cutaneous diseases (i.e. psoriasis, psoriatic arthritis and hidradenitis suppurativa), skin cancers (e.g. squamous cell carcinoma, basal cell carcinoma and melanoma) and targeted therapies (i.e. etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, tildrakizumab, guselkumab and risankizumab) and chemically synthetized drugs (e.g. apremilast and tofacitinib) as targeted therapies has improved the management of these diseases (16–18). However, since these drugs target molecules that may be relevant to cancer immunosurveillance mechanisms, some concerns were raised about their association with an increased risk of cancer occurrence (19–23). A recent meta-analysis of randomized clinical trials (RCTs) and open-label extension (OLE) studies reported that TNF inhibitors are associated with an increased risk of non-melanoma skin cancers (NMSC) in people with psoriasis. However, the authors of this study found that no real-world evidence was available and acknowledged the significant limitations associated with the study design of the articles included, that make it difficult to extrapolate to real-world practice (24). Evidence on the risk of skin cancer in patients with chronic inflammatory cutaneous diseases on targeted therapies is still sparse controversial. Therefore, the aim of this systematic review and meta-analysis was to assess the risk of cutaneous malignancies in patients with psoriasis, psoriatic arthritis or hidradenitis suppurativa treated with targeted therapies.

Data Extraction

For eligible studies, information on the following items was independently collected by the same two authors and stratified by skin cancer type: study authors, year of publication, catchment area, data source, study population, study years, study design and risk estimate. Any disagreements were resolved by consensus with a third independent assessor (GT or CG).

Assessment of Risk of Bias and Overall Quality of the Evidence

The risk of bias of the observational studies included in this systematic review was independently assessed by two authors (SC and FC) using the Newcastle-Ottawa quality assessment scale (25). This instrument consists of eight different domains for cohort studies (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study, comparability of cohorts on the basis of the design or analysis, assessment of outcome, follow-up long enough for outcomes to occur, adequacy of follow up) and case-control studies (adequate case definition, representativeness of the cases, selection of controls, definition of controls, comparability of cases and controls on the basis of the design or analysis, ascertainment of exposure, same method of ascertainment for cases and controls, non-response rate). The included studies were categorized as “low risk of bias” if at least six of the eight domains were judged to be at low risk of bias.

Statistical Analysis

For each included study, skin cancer incidence rates (IR) per 10,000 person-years (PY) were considered as the primary
outcome for the meta-analysis. Meta-analysis of IRs was performed assuming that the logarithm of each study-specific rate was normally distributed and the corresponding standard error, used to perform the inverse-variance weighting, was computed from the 95% CI (or p-value) reported in the original IRs. Between-study heterogeneity of the estimates was assessed using the Cochran’s Q-test (26) along with its derived measure of inconsistency (I²), and was considered to be present when Cochran’s Q-test p-value was < 0.10 or I² > 40% (27). Estimates were summarized by fixed-effects or random-effects models, according to the absence or the presence of heterogeneity, respectively. It is generally accepted that when there are fewer than ten studies in a meta-analysis, both meta-regression (27) and test for publication bias (28) should not be considered. Both the study specific as well as the pooled epidemiological estimates, were graphically depicted, with their 95% CI, on a forest plot. Analyses were stratified for specific skin cancer types, i.e. NMSCs and melanoma. If a study presented more than one estimate, the most recent one was used. Two-sided p-values<0.05 were considered for statistical significance. All calculations were carried out using R Foundation for Statistical Computing (version 4.0, package: metafor).

RESULTS

Characteristics of the Studies Included

The original electronic search yielded 1762 (1549 after removing duplicates) papers potentially relevant for this review (Figure 1). After removing duplicates, 1549 were initially screened. Of these, 1467 were excluded after the screening of study titles and abstracts. The remaining 82 studies were retrieved for more detailed evaluation and 10 of them met the review inclusion criteria. The main characteristics of the included studies are reported in Table 1. Most of the included studies were prospective cohort studies (N= 5; 50.0%) (33–36, 38), three (30.0%) (29, 31, 32) were retrospective cohort studies, one was...
| Reference | Catchment area | Data source | Study population | Study drugs | Study years | Study design | IR per 10,000 PYs [95%CI] |
|-----------|----------------|-------------|------------------|-------------|-------------|--------------|------------------------|
| **Non-melanoma skin cancer** | | | | | | | |
| 29 | California (USA) | Kaiser Permanente Northern California (KPNC) | All KPNC members aged ≥ 18 years, diagnosed with psoriasis between 1998 and 2011 and treated with a systemic antipsoriatic agent | Adalimumab, etanercept, infliximab, ustekinumab | 1998-2011 | Retrospective cohort study | 120 [98-143] |
| 30 | USA | US Truven MarketScan database | Patients with moderate to severe PsA, defined by ≥1 inpatient or ≥2 outpatient diagnosis codes on 2 unique calendar days | Adalimumab, etanercept, infliximab, apremilast | 2010-2015 | Clinical trial and real-world data comparison | 149.3 [116.5-182.0] |
| 31 | United Kingdom | British Society for Rheumatology Biologics Register + National cancer and death registers | All patients diagnosed with PsA starting a TNF-inhibitor and registered in the British Society for Rheumatology Biologics Register | Etanercept, adalimumab, infliximab | 2002-2012 | Retrospective cohort study | N.A. |
| 32 | USA | MarketScan®, database and Medicare | Patients with a diagnosis of psoriasis, with the first outpatient qualifying ICD-9 CM code | Etanercept | 2005-2009 | Retrospective cohort study | 185.8 [160.2-211.42] |
| 33 | USA, Canada, Germany, France, Czech Republic, Greece, Netherlands, Spain, UK, Austria, Denmark, Ireland, Sweden | ESPRIT Registry | Patients aged ≥ 18 years of age with chronic plaque psoriasis who had been prescribed adalimumab | Adalimumab | 2008-2015 | Prospective cohort study | 62 [52-72] |
| 34 | Canada | OBSERVE-5 surveillance registry | Adult patients with moderate to severe psoriasis initiating etanercept | Etanercept | 2006-2012 | Prospective cohort study | 125 [60-240] |
| 35 | USA | OBSERVE-5 surveillance registry | Adult patients with moderate to severe psoriasis initiating etanercept | Etanercept | 2006-2012 | Prospective cohort study | 262 [220-310] |
| 36 | Germany | The German Psoriasis Registry PsoBest | Adult patients with moderate-to-severe psoriasis at the time point of a new drug to be started | TNF-α inhibitors | 2008-2012 | Prospective cohort study | 38 [12-90] |
| 36 | Germany | The German Psoriasis Registry PsoBest | Adult patients with moderate-to-severe psoriasis at the time point of a new drug to be started | Ustekinumab | 2008-2012 | Prospective cohort study | 4 [10-138] |
| 36 | The Netherlands | Radboud University Nijmegen Medical Centre pharmacovigilance registry | Patients starting biological treatment for psoriasis in the Dermatology outpatient clinic of the Radboud University Nijmegen Medical Centre | Etanercept, adalimumab, infliximab, ustekinumab | 2005-2010 | Prospective cohort study | N.A. |

**Melanoma**

| Reference | Catchment area | Data source | Study population | Study drugs | Study years | Study design | IR per 10,000 PYs [95%CI] |
|-----------|----------------|-------------|------------------|-------------|-------------|--------------|------------------------|
| 29 | California (USA) | Kaiser Permanente Northern California (KPNC) | All KPNC members aged ≥ 18 years old, diagnosed with psoriasis between 1998 and 2011 and treated with a systemic antipsoriatic agent | Adalimumab, etanercept, infliximab, ustekinumab | 1998-2011 | Retrospective cohort study | 8 [3-14] |
| 31 | United Kingdom | British Society for Rheumatology Biologics Register + National cancer and death registers | All patients diagnosed with PsA starting a TNF-inhibitor and registered in the British Society for Rheumatology Biologics Register | Etanercept, adalimumab, infliximab | 2002-2012 | Retrospective cohort study | N.A. |
| 37 | America and Europe | Psoriasis Longitudinal Assessment and Registry (PSOLAR) | Patients aged ≥ 18 years with moderate-to-severe psoriasis who were receiving, or were candidates to receive, systemic therapy | TNF-α inhibitors | 2007-2015 | Nested case-control study | N.A. |
| 37 | America and Europe | Psoriasis Longitudinal Assessment and Registry (PSOLAR) | Patients aged ≥ 18 years with moderate-to-severe psoriasis who were receiving, or were candidates to receive, systemic therapy | Ustekinumab | 2007-2015 | Nested case-control study | N.A. |

(Continued)
a nested case-control study (10.0%) (37) and one was a study comparing clinical trials data and real-world data (10.0%) (30).

All included studies focused on the incidence of skin malignancies in patients treated with TNF-α inhibitors, three of them included also patients treated with ustekinumab (29, 35, 36) and only one study reported NMSC IRs also for apremilast and tofacitinib (30). No observational studies assessing the incidence of skin cancer in patients with inflammatory cutaneous diseases and treated with secukinumab, ixekizumab, brodalumab, tildrakizumab or risankizumab were found. All the included studies used real-world data sources, such as drug or disease registries and claims databases.

Of the 10 studies included in this systematic review, 7 provided data suitable for meta-analysis.

Risk of Bias in Individual Studies

Figure 2 summarizes the risk of bias assessment of individual studies. The overall risk of bias was rated as low for 7 (29, 30, 32–34, 35, 38) of the 10 included studies, while 3 (31, 36, 37) studies...
proved to have an unclear risk of bias. Limitations mainly concerned the assessment of the presence or absence of prognostic factors and the adequacy of follow-up.

Targeted Therapies and Skin Cancer Incidence Rates
IRs of NMSC and melanoma reported in the articles included in this systematic review are summarized in Figure 3.

Overall, the IR of NMSC in the included studies ranged from 38 (95% CI: 12-90) (35) to 262 (95% CI: 220-310) (34) cases per 10,000 PYs. The pooled IR for the overall risk of NMSC was 124.5 (95% CI 83.4 – 185.8) per 10,000 PYs. A considerable heterogeneity was found among these studies (Cochrane’s Q = 173.0; I² = 96.5%).

A comparison of the incidence ratio for the overall risk of NMSC in patients exposed to biologics and small molecules versus non-biologic drugs users could be obtained only in two studies (29, 36). In one case (36), the hazard ratio (HR) was 1.42 (95% CI:1.12-1.80), while in the other one the Incidence Rate Ratio (IRR) was 0.74 (95% CI:0.60-0.91) (29).

The IR of melanoma in the included studies ranged from 5 (95% CI: 3-10) (38) to 8 (95% CI: 0-43) (35) cases per 10,000 PYs. The pooled IR for the overall risk of melanoma was 6.1 (95% CI 3.9 – 9.6) per 10,000 PYs. No heterogeneity among studies reporting melanoma IRs was found (Cochrane’s Q= 1.0; I² = 0.0%). The only study reporting an HR for melanoma between users of biologic drugs and small molecules versus non-biologic users (36) showed no statistically significant difference (HR:1.57, 95% CI: 0.61-4.09).

It was not possible to investigate both the source of heterogeneity and the presence of publication bias, as fewer than ten studies were included in the meta-analysis (28).

DISCUSSION
In recent years, we have witnessed a revolution in the treatment of many skin diseases, ranging from bullous diseases, urticaria, atopic dermatitis, to hidradenitis suppurativa and psoriasis (39). In particular, psoriasis is a chronic cutaneous inflammatory disease affecting an estimated 125 million people worldwide, that is often associated with systemic manifestations such as major adverse cardiovascular event, obesity, inflammatory bowel disease and arthropathic psoriasis (40, 41). The decision to use one therapy over another is significantly influenced by these comorbidities and the severity of the disease. Moreover, a better understanding of the pathogenesis of this systemic disease had led to identification of new therapeutic targets (42). Whereas the older treatment options, such as phototherapy, methotrexate and cyclosporine A, are still effective, biotechnological drugs are substantially improving the therapeutic arsenal. The success of these new therapies lies in their great selectivity of action which allows to obtain, in most cases, a significant therapeutic efficacy in a short time with a reduction in side effects compared to traditional therapies. Through these therapies, even the severest symptoms of psoriasis and psoriatic arthritis can be excellently treated (43, 44). The biological drugs produced so far are...
monoclonal antibodies and fusion proteins. These products have the enormous advantage of being able to selectively interfere, at various levels and with different modes of action, in the immunological processes that trigger and sustain psoriasis (45). To date they are divided into five classes: TNF-α inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, IL-23 inhibitors and phosphodiesterase type 4 (PDE4) inhibitors (40).

According to the above-mentioned results, our review found no observational studies assessing the incidence of skin cancer in patients with inflammatory cutaneous diseases and treated with biologics targeting selectively IL-17 or IL-23, thus obtaining mainly data on patients under anti-TNF-α therapy and, to a more limited degree, under ustekinumab, apremilast and tofacitinib.

TNF-α inhibitors infliximab, etanercept, adalimumab and certolizumab pegol are the oldest class of currently approved biotechnological drugs for the treatment of both psoriasis and psoriatic arthritis and, limited to adalimumab, of hidradenitis suppurativa. TNF-α exerts several effects. It could promote the progression of cancer (46), but also blocking TNF-α could result in arresting antitumor immune response and in promoting the growth of immunogenic tumors (47–49).

Some of the studies analyzed in this systematic review also included patients receiving ustekinumab, apremilast and tofacitinib (29, 30, 35, 36). Ustekinumab belongs to the class of biologics targeting the IL-12/23 pathway, whereas apremilast is an anti-PDE4 small molecule and tofacitinib a janus kinase inhibitor. The inhibition of these pathways causes a downregulation of the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17 and other inflammatory cytokines, all involved at least in part in the tumorigenesis.

Consequently, whereas these drugs have shown dramatically excellent efficacy, concerns have been raised about the risks related to this class of agents.

Undoubtedly, patients with psoriasis are at an increased risk of cancer. Assessing the baseline risk of cutaneous malignancies in psoriasis patients is challenging due to most studies including both treated and untreated patients, and due to confounding factors like phototherapy and immunosuppressive therapy (50). Moreover NMSC and melanoma are known to arise with increased incidence among patients that have undergone medical radiation procedures or immunosuppressive therapy (51–53), such as those immunosuppressed in an iatrogenic way after a solid organ transplantation (54–56). According to the World Health Organization, age standardized world incidence of melanoma and NMSC are respectively 3.4 and 11 per 100,000 PYs. On the other hand, recent data emerging from literature show that skin cancers have a higher incidence in psoriasis patients than general population with a standardized incidence ratio of 3.37 (95% CI 1.84-5.66) (57). More in detail, Pouplard et al. in a meta-analysis reported a standardized incidence ratio of 5.3 for squamous cell carcinoma (SCC) (95% CI 2.63–10.71) and of 2.00 for basal cell carcinoma (BCC) (95% CI 1.83–2.20), whereas the authors reported a similar risk of melanoma in psoriatic patients compared to the general populations.

When considering the risk of skin cancer in psoriatic patients under treatment, many aspects should be analyzed: predisposing factors, duration and timing of exposure, the cumulative dose, the interaction with other carcinogens and, also, the latency. Despite all these data to be considered, enough evidence confirmed the relation between skin cancer and specific treatment for psoriasis and it has emerged that the risk increases even more respect untreated patients (58).

In particular, oral psoralen and ultraviolet A (PUVA) is associated with an increased risk for skin cancer in a dose dependent fashion: risk of NMSC is greatest with >350 treatments, while melanoma risk is increased with >250 treatments (59, 60). However, the carcinogenic mechanism of PUVA has not been elucidated: it maybe acts in a mutagenic and immunologic way (61). Instead, even if UVB phototherapy may increase photoaging acting with multiple mechanisms (inhibition of DNA synthesis, epidermal keratinocyte hyperproliferation, induction of T-cell apoptosis and of anti-inflammatory cytokines), no increase in skin cancer has been observed, especially with <100 treatments. Only when patients have been treated previously with PUVA and, in a second time, with broadband UVB (>300 treatments), it has been noted a modest increase in SCC (incidence rate ratio 1.37, 95% CI 1.03–1.83) and BCC (incidence rate ratio 1.45, 95% CI 1.07–1.96) (62).

Also systemic non biologic therapies are associated with an increased risk of skin cancers (63), acting primarily as immunosuppressants. Treatment with methotrexate results in higher risk for NMSC, but no association with risk for melanoma was observed (64). In detail, it has been shown that patients in treatment with methotrexate seem to have a doubled risk of SCC compared with people who receive PUVA therapy (65). Cyclosporine is associated with an elevated risk of SCC, which could increase even more in relation to treatment duration (>2 years) and previous therapy (PUVA) (66, 67), as already seen in transplant patients treated with high doses of cyclosporine and for long periods (68–70).

In our systematic review, we also considered studies evaluating the risk of skin cancers in patients with hidradenitis suppurativa in treatment with adalimumab, the only approved biologic agent for moderate-to-severe hidradenitis (71, 72). No articles were found that met the inclusion criteria. Nevertheless, data from literature point to a higher risk of developing NMSC in patients with hidradenitis than general population (15). Compared with psoriatic patients who underwent biologic treatment, patients with hidradenitis start treatment with TNF-α inhibitors after fewer months/years from the diagnosis of the disease and the guidelines do not provide obligatory treatment with first line systemic immunosuppressive drug, such as cyclosporine or methotrexate, before approaching the biologic therapy.

Considering all together the studies included in the metanalysis, the IR emerging from our systematic review shows an incidence of skin cancer in biologic treated patients, 124.5 per 10000 PYs for NMSC and 6.1 per 10000 PYs for melanoma. With regard to NMSC, IRs in literature presented large variability, from 24 in a psoriatic cohort of a German registry to 262 coming from a USA surveillance registry on patients treated with etanercept. The IR has been established on 8 out of 10 studies (Table 1). Concerning melanoma, 3 out of 6 studies reported an IR, ranging from 5 to 8 (Table 1). As a
comparison, these IRs are significantly lower than post-transplant skin cancer IR, that is 1355 per 100,000 PYs for melanoma (73).

Our figures substantially agree with those reported in a recent systematic review and metaanalysis by Vaengebjerg et al. (14) who reviewed 112 observational studies and more than 2 million persons, thus assessing them for prevalence, incidence and overall risk of cancer in patients with psoriasis and psoriatic arthritis. The reported IR per 1000 PY for overall cancer was 11.75 (95% CI, 8.66-15.31) and 4.35 (95% CI, 3.18-5.70) for keratinocyte cancer, whereas the IR for melanoma was 0.37 per 1000 PYs.

A study by Esse and collaborators was focused on melanoma in patients treated with biologics for common inflammatory diseases, such as inflammatory bowel diseases, rheumatoid arthritis and psoriasis (68). In detail, they considered a total of 7 studies, consisting of patients treated with TNF-α inhibitors, one of which regarding patients with psoriasis and, moreover, included in our review (74). According with their findings, the risk of melanoma in biologic-treated patients with IBD and psoriasis compared with their biologic-naïve counterparts receiving conventional systemic therapy showed no statistically significant increases. Esse et al. included in their paper only one study (36) concerning psoriatic patients; this study is currently the only one reporting an HR for melanoma in patients treated with TNF-α inhibitors compared with non-biologic users and shows no significant difference between the two groups.

With regard to NMSC, the paper by Asgari (36) explicitly reported an HR for the same comparison. Our review considered an additional study in which we were able to calculate IRR from the reported data (29). While Asgari et al. (36) reported an increased HR for NMSC in patients treated with TNF-α inhibitors compared with non-biologic users, data coming from the other study (29) showed no statistically significant differences.

The main strengths of our analysis included the use of a well-defined protocol with strict inclusion and exclusion criteria. Complying with the protocol, our search addressed a clearly focused question with standardized data extraction and quality assessment to minimize errors. In addition, the real-world setting of the studies, the inclusion of biologic agents and of patients treated exclusively for common cutaneous inflammatory diseases represent distinctive features of our review and metaanalysis.

The main limitation was the small number of eligible studies. The studies were also heterogeneous, which makes comparison difficult. In addition, a major weakness of the analysis was the absence of adjustment for established risk factors for NMSC and melanoma.

Furthermore, in previous studies performed only on patients with PSO it was found that there were no univocal data on the higher or lower incidence of tumors in patients with PSO. In particular, they were studies that analyzed both patients treated with systemic drugs and patients treated with biological drugs (50, 75). In our systematic review and meta-analysis, we considered only patients treated with target therapies suffering from psoriasis, PSA and/or HS.

In common with previous studies, on the other hand, there is the fact that the risk of skin tumors itself cannot be excluded because patients had to undergo immunosuppressive therapy (systemic or not) before being able to carry out treatment with a target therapy. Another limit that emerges from our systematic review, in common with other articles already present in the literature, is the follow-up time. As demonstrated by many studies, the development and growth times of skin tumors are long and may exceed the observation periods of the clinical trials in the literature.

SUMMARY AND PERSPECTIVES

Although with some limitations, the metaanalysis of currently available real-world data seems to suggest that treatment of psoriasis, psoriatic arthritis and/or hidradenitis suppurativa with TNF-α inhibitors, ustekinumab, apremilast or tofacitinib does not increase the risk of NMSC or melanoma compared to “non-biologic” systemic treatments. The cumulative sample size of the studies in literature is certainly conspicuous, but, in the light of the worldwide diffusion and frequency of the aforementioned diseases as well as their multifactorial nature and response to treatment, including undesired effects, further data are desirable.

Additionally, the ending years of the periods analyzed in the available studies range from 2009 to 2015. Similar evaluations of real-world evidence concerning molecules marketed in the last 10-15 years, such as secukinumab, ixekizumab, brodalumab, tildrakizumab or risankizumab, would be of great interest, particularly when considering that these molecules are widely used in current clinical practice. Consequently, to conduct future trials it is necessary to consider the above data and the fact that the number of studies comparing newer molecules and conventional drugs are small. A greater number of new trials will have to be conducted, considering longer follow-up times and, above all, common methods will have to be applied to allow a comparison between the various studies.

In summary, this updated systematic review and meta-analysis seems to suggest that no differences exist between treatment of chronic cutaneous diseases with biotechnological drugs/small molecules and conventional DMARDs in terms of HR/IRR for melanoma, while data on NMSC are more controversial. Nevertheless, periodic dermatologic screening should be ensured for all patients undergoing these therapies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualization: CG and SC. Methodology: SC, FC, GT, LB, and CG. Validation: SC, LB, and CG. Resources: SC, AF, FC, GT, YI, LB, MB, and CG. Data curation: SC, AF, FC, YI, GT, MB, and CG. Writing—original draft preparation: SC, LB, and CG. Writing—review and editing: SC, LB, and CG. Supervision: SC, LB, and CG. All authors contributed to the article and approved the submitted version.
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REFERENCES

1. Van Der Zee HH, De Ruiter L, Van Den Broecke DG, Dik WA, Laman JD, Prens EP. Elevated Levels of Tumour Necrosis Factor (TNF)-α, Interleukin (IL)-1β and IL-10 in Hidradenitis Suppurativa Skin: A Rationale for Targeting TNF-α and IL-1β. Br J Dermatol (2011) 164:1292–8. doi: 10.1111/j.1365-2133.2011.09225.x

2. Kelly G, Hughes R, McGarry T, Van Den Born M, Evans H, et al. Dysregulated Cytokine Expression in Lesional and Nonlesional Skin in Hidradenitis Suppurativa. Br J Dermatol (2015) 173:1431–9. doi: 10.1111/bjd.14075

3. Menon B, Gullick NJ, Walter GJ, Rajasekhar M, Garwood T, Evans H, et al. Interleukin-17+CD8+ T Cells Are Enriched in the Joints of Patients With Psoriatic Arthritis and Correlate With Disease Activity and Joint Damage Progression. Arthritis Rheumatol (2014) 66:1272–81. doi: 10.1002/art.38376

4. Nickoloff BJ, Qin JZ, Nestle FO. Immunopathogenesis of Psoriasis. Clin Rev Allergy Immunol (2007) 33:45–56. doi: 10.1007/s12016-007-0039-2

5. Sabat R, Philipp S, Höflisch C, Kreutzscher S, Wallace E, Asadullah K, et al. Immunopathogenesis of Psoriasis. Exp Dermatol (2007) 16:779–88. doi: 10.1111/j.1600-0625.2007.00629.x

6. Gisondi P, Talamonti M, Chiricozzi A, Piaserico S, Amerio P, Balato A, et al. Treat-to-Target Approach for the Management of Patients With Moderate-to-Severe Plaque Psoriasis: Consensus Recommendations. Dermatol Ther (Heidelb) (2021) 11:235–52. doi: 10.1007/s13555-020-00475-8

7. Cecarelli M, Venanzi Rullo E, Vaccaro M, Facioli A, d’Aleo F, Paolucci IA, et al. HIV-Associated Psoriasis: Epidemiology, Pathogenesis, and Management. Dermatol Ther (2019) 32(2):e12806. doi: 10.1111/dth.12806

8. Shapter E, Weitzman SA. Chronic Inflammation and Cancer. Oncology (Williston Park) (2002) 16(2):217–26. doi: 10.2101/bj2696-15

9. Tchernev G, Guarneri C, Bevelacqua V, Wollina U. Carcinoma Cuniculatum in Course of Ectasic Conglutition: Blocking Autoimmunity But Propagation of Cancerogenesis? Int J Immunopathol Pharmacol (2014) 27:261–6. doi: 10.1177/03946302145200213

10. Lapins J, Ye W, Nyren O, Emestam L. Incidence of Cancer Among Patients With Hidradenitis Suppurativa. Arch Dermatol (2001) 137:730–4. doi: 10.1001/archdermatol.137.7.730

11. Rastogi S, Patel KR, Singam V, Ali Y, Gao J, Amin A, et al. Vulvar Cancer Risk in 892 Women With Hidradenitis Suppurativa and Hidradenitis Suppurativa Carcinoma in Korea: A Nationwide Population-Based Cohort Study. J Dermatol (2019) 46:95–102. doi: 10.1111/1346-8138.14998

12. Malaponte G, Signorelli SS, Bevelacqua V, Polese J, Taborelli M, Guarneri C, et al. Increased Levels of NF-κB- and IL-1β. PLoS One (2015) 10(7):e0132496. doi: 10.1371/journal.pone.0132496

13. Auvegebberg S, Skov L, Egeberg A, Loft ND. Prevalence, Incidence, and Risk of Cancer in Patients With Psoriasis and Psoriatic Arthritis: A Systematic Review and Meta-Analysis. JAMA Dermatol (2020) 156:808–10. doi: 10.1001/jamadermatol.2020.0024

14. Jung JM, Lee KH, Kim YJ, Chang SE, Lee MW, Choi JH, et al. Assessment of Overall and Specific Cancer Risks in Patients With Hidradenitis Suppurativa. JAMA Dermatol (2020) 156:844–53. doi: 10.1001/jamadermatol.2020.1422

15. Di Lernia V, Neri I, Pintonon PC, Di Nuzzo S, Stingeni L, Guarneri C, et al. Treatment Patterns With Systemic Antipsoriatic Agents in Childhood Psoriasis: An Italian Database Analysis. G Ital di Dermatologia e Venereol (2017) 152:327–32. doi: 10.23736/s0392-0488.16.05287-X

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.687432/full#supplementary-material
Overexpression. *Biochim Biophys Acta - Mol Cell Res* (2016) 1863:483–9. doi: 10.1016/j.bbamcr.2015.09.018
70. D’Aniello C, Perri F, Scarpati GDV, Pepa CD, Picarelli V, et al. Melanoma Adjuvant Treatment: Current Insight and Clinical Features. *Curr Cancer Drug Targets* (2017) 18:442–56. doi: 10.2174/1568009617666170208163714
71. Flood KS, Porter ML, Kimball AB. Biologic Treatment for Hidradenitis Suppurativa. *Am J Clin Dermatol* (2019) 20:625–38. doi: 10.1007/s40257-019-00439-5
72. Giuffrida R, Cannavò SP, Coppola M, Guarneri C. Novel Therapeutic Approaches and Targets for the Treatment of Hidradenitis Suppurativa. *Curr Pharm Biotechnol* (2020) 22:59–72. doi: 10.2174/13892010216661200505100556
73. Garrett GL, Blanc PD, Boschadin J, Lloyd AA, Ahmed RL, Anthony T, et al. Incidence of and Risk Factors for Skin Cancer in Organ Transplant Recipients in the United States. *JAMA Dermatol* (2017) 153:296–303. doi: 10.1001/jamadermatol.2016.4920
74. Esse S, Mason KJ, Green AC, Warren RB. Melanoma Risk in Patients Treated With Biologic Therapy for Common Inflammatory Diseases: A Systematic Review and Meta-Analysis. *JAMA Dermatol* (2020) 156:787–94. doi: 10.1001/jamadermatol.2020.1300
75. Reddy SP, Martires K, Wu JJ. The Risk of Melanoma and Hematologic Cancers in Patients With Psoriasis. *J Am Acad Dermatol* (2017) 76:639–647.e2. doi: 10.1016/j.jaad.2016.09.047

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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