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Psoriasis and psoriasiform reactions secondary to immune checkpoint inhibitors

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Abstract

The advent of Immune Checkpoint Inhibitors (ICIs) as a standard of care for several cancers, including melanoma and head/neck squamous cell carcinoma has changed the therapeutic approach to these conditions, drawing at the same time the attention on some safety issues related to their use. To assess the incidence of psoriasis as a specific immune-related cutaneous adverse event attributing to ICIs using the Eudravigilance reporting system. All reports of adverse drug reactions (ADRs) concerning either exacerbation of psoriasis or de novo onset of psoriasis/psoriasiform reactions associated to the use of Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) inhibitors ipilimumab and tremelimumab, and the Programmed cell Death protein 1/Programmed Death-Ligand 1 (PD-1/PD-L1) inhibitors nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, and cemiplimab were identified and extracted from the Eudravigilance reporting system, during the period between the date of market licensing (for each study drug) and 30 October 2020. 8213 reports of cutaneous ADRs associated with at least one of study drug have been recorded, of which 315 (3.8%) reporting psoriasis and/or psoriasiform reactions as ADR. In 70.8% of reports patients had pre-existing disease. ICIs-related skin toxicity is a well-established phenomenon, presenting with several conditions, sustained by an immune background based on the activity of some cells (CD4+/CD8+ T-cells, neutrophils, eosinophils, and plasmocytes), inflammatory mediators, chemokines, and tumor-specific antibodies. In this setting, psoriasis represents probably the most paradigmatic model of these reactions, thus requiring adequate recognition as no guidelines on management are now available.

KEYWORDS
adverse drug reactions, cancer, immune checkpoint inhibitors, melanoma, psoriasis

1 | INTRODUCTION

Immune Checkpoints Inhibitors (ICIs) represent a new group of monoclonal antibodies that proved to be effective on several malignancies by blocking specific targets such as Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) and Programmed cell Death protein 1 (PD-1)/Programmed Death-Ligand 1 (PD-L1).[1]

ICIs are characterized by a common pathway of action. They cause cytotoxic T-cell activation and enhance tumor cells destruction.[2,3]

Gianluca Trifirò and Claudio Guarneri have contributed equally to this study.

Along with tremelimumab, ipilimumab is a recombinant human monoclonal IgG1 antibody acting against CTLA-4, a protein expressed in activated T cells. As CTLA-4 promotes inhibition of the immune response, the net action of these two drugs consists in the increasing activation and proliferation of T-lymphocytes by blocking the interaction of CTLA-4 with its ligands CD80 and CD86. Since 2011, ipilimumab was approved for the treatment of unresectable or metastatic melanoma and renal cell carcinoma.[4]

Nivolumab and pembrolizumab have been approved as monotherapy or in combination with other drugs for the treatment of melanoma, head and neck squamous cell carcinoma, renal cell carcinoma, lung cancer (small cell and nonsmall cell types), and other neoplasms.[5-8] They are human monoclonal IgG4 antibodies targeting the PD-1 receptor, which promotes the activity of specific T-lymphocytes both in peripheral and tumor tissues.

Atezolizumab, durvalumab, and avelumab are PD-L1 protein inhibitors that have been recently approved in Italy for the treatment of metastatic nonsmall-cell lung cancer, locally advanced or metastatic urothelial carcinoma, extensive-stage small-cell lung cancer, and metastatic Merkel cell carcinoma.[9,10] Cemiplimab has been authorized as monotherapy for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC), who are not candidates for curative surgery or radiation (Table 1).

Because of the wide and growing use of these products, relevant safety concerns are emerging during the last years. Based on the potential effect on the immune response and the available evidence coming from randomized clinical trials, registries and medical literature reports, more than 60% of patients treated with ICIs develop several adverse effects, affecting a lot of body systems.[11-14]

TABLE 1 Date of marketing authorization and description of approved therapeutic indications for the immune checkpoint inhibitors included in the study

ICI	Target	Date of EMA approval	Therapeutic indications approved by EMA
Ipilimumab	CTLA-4	07/2011	• Metastatic or unresectable melanoma • Advanced renal cell carcinoma • Nonsmall cell lung cancer (NSCLC)/metastatic NSCLC
Nivolumab	PD-1	06/2015	• Metastatic or unresectable melanoma (also with ipilimumab) • Nonsmall cell lung cancer (NSCLC) • Advanced renal cell carcinoma • Classical Hodgkin lymphoma • Recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN); • Locally advanced or metastatic urothelial carcinoma
Pembrolizumab	PD-1	07/2015	• Metastatic or unresectable melanoma • Nonsmall cell lung cancer (NSCLC • Classical Hodgkin lymphoma • Locally advanced or metastatic urothelial carcinoma • Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), • Renal cell carcinoma
Atezolizumab	PD-L1	09/2017	• Locally advanced or metastatic urothelial carcinoma • Metastatic nonsmall cell lung cancer (NSCLC) • Extensive -stage small cell lung cancer (ES-SCLC) • Triple-negative breast cancer
Avelumab	PD-L1	09/2017	• Metastatic Merkel cell carcinoma • Advanced renal cell carcinoma (plus axitinib)
Durvalumab	PD-L1	09/2018	• Locally advanced, unresectable nonsmall cell lung cancer (NSCLC) • Extensive-stage small cell lung cancer (ES-SCLC) (in combination with etoposide and either carboplatin or cisplatin)
Cemiplimab	PD-1	06/2019	• Locally advanced or metastatic cutaneous squamous cell carcinoma
Tremelimumab	CTLA-4	07/2019	• Malignant neoplasms (excluding central nervous system, hematopoietic and lymphoid tissue neoplasms) • Malignant neoplasms of hematopoietic and lymphoid tissue

Concerning the skin, more than 30% of reports are characterized by mild cutaneous toxicity, alone or associated with other symptoms.[14] A possible etiopathogenic explanation of these "specific" reactions is the overall stimulation of the immune system against the tumor cells induced by ICIs. Indeed, inhibition of CTLA-4 promotes CD4+ and CD8+ function as well as PD-1 and PD-1 ligands are expressed in immune cells including activated T lymphocytes, B lymphocytes, dendritic cells, and macrophages. Although it has been not yet fully elucidated, the above-mentioned drugs could act as a trigger of autoimmunity, particularly at the skin level.[1,2,13,14,15]

Several skin conditions have been associated with ICIs, including alopecia areata, vitiligo, pyoderma gangrenosum, erythema nodosum, prurigo nodularis, Sweet's syndrome, Sjogren syndrome, dermatomyositis, sarcoidosis, lichen, and psoriasis, but also urticaria, rosacea, rashes, and pruritus.[13,16,17]

Chronic plaque psoriasis or other clinical phenotypes (erythrodermic, pustular, guttate, palmoplantar, scalp/nail, and inverse psoriasis) have been attributed to ICI treatment, as a recrudescence of an existing disease or as a new-onset form.[18,19] According with the pathogenesis of psoriasis, PD-1 inhibition could strongly impact the Th1/Th17 pathways, leading to IL-17 overexpression and to the typical inflammatory cascade with the antitumor activity.[20-22]

The purpose of this paper is to briefly review ICI-related reports from the Eudravigilance reporting system during the period 2011 to 2020 concerning with psoriasis and psoriatic adverse drug reactions and to better characterize the incidence of this skin toxicities, thus providing recommendations for their management.

2 | METHODS

For our research, we used the public version of Eudravigilance database (http://www.adrreports.eu/en/search.html). This website was founded by the European Medicines Agency (EMA) in 2012 to provide public access to reports of suspected side effects/adverse drug reactions. These reports are submitted electronically by national medicines regulatory authorities and by pharmaceutical companies that hold marketing licenses for the medicines.

All cutaneous ADR reports related to ipilimumab, tremelimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab and cemiplimab particularly if manifesting as psoriasis or psoriasiform dermatitis, were considered since their market authorization by EMA to 30 October 2020. According with the website searching options, we selected "suspected adverse drug reaction reports for substances" then browsing the name of each of the drugs and MedDRA PT term "psoriasis" among "Skin and subcutaneous tissue disorders". Furthermore, line-listing including more clinical data about selected ADR reports were examined in detail.

The data were collected with no limitation for seriousness of the reaction, geographic origin, sex or age group of the patients.

Tremelimumab was approved for use only in the second half of 2019 and no psoriasis/psoriasiform ADRs are still available in the database. Similarly, cemiplimab has been marketed in 2019 and only two cases were documented in Eudravigilance. Durvalumab, atezolizumab and avelumab were licensed between the late 2017 and the end of 2018 and few reports of such reactions have been reported. The main part of psoriatic ADRs were related to nivolumab and pembrolizumab, with few cases on ipilimumab (Table 1).

3 | RESULTS

Overall, 8213 ADR reports regarding skin and subcutaneous tissue disorders associated with ICIs were collected in the EudraVigilance reporting system during the study period. Of these, 315 (3.8%) reported psoriasis as ICI-related ADR, occurring de novo or as a recurrence in previously diagnosed patients.

ICI-related psoriasis reports more frequently concern males (234 out of 307; 75.9%) in the age range 65 to 85 years (145 out of 217; 66.3%). In the majority of reports in which such clinical data are available (N = 118; 70.2%) psoriasis presents more as a new flare in patients with pre-existing disease than as a new-onset disease and patients were mainly treated with topical steroids for these adverse reactions (102 out of 138; 73.9%).

With regard to the type and seriousness of the psoriatic adverse reactions there are no detailed information available in the reporting system. The outcome was "unknown" in 124 cases (39.3%) whereas a total of 138 (44.1%) of cases were generally considered "recovered/resolved" (N = 60) or "recovering/resolving" (N = 78); only two cases (0.6%) were resolved "with sequelae" while N = 51 cases (16%) were "not recovered/not resolved."

Among individual compounds, the most frequently reported ICI was nivolumab (N = 175; 55.9%), followed by pembrolizumab (N = 104; 33.2%), atezolizumab (N = 15; 4.8%), ipilimumab (N = 12; 3.8%), cemiplimab (N = 2; 0.6%), and avelumab (N = 1; 0.3%). In N = 7 reports nivolumab and ipilimumab were co-administered.

Psoriasis represents only the 0.8% (12 out of 1476) of the total number of cutaneous ADRs associated to ipilimumab and 2.9% of those associated to avelumab (only one case report out of 34), vs 3.7% (6 out of 160) with durvalumab, 4.1% (104 out of 2532) with pembrolizumab, 4.4% (145 out of 341) with atezolizumab, 4.8% with nivolumab (175 out of 3668), and 4.9% (two out of 41) with cemiplimab.

Except for durvalumab related-psoriasis, affecting four females out of six patients, this adverse reaction occurs mainly in males (with percentages ranging from 71.1% observed for pembrolizumab to 83.3% observed for ipilimumab).

ICI related-psoriasis affected more frequently older people than other cutaneous ADRs: 66.4% in the 65/85 years group vs 54.6% of other cutaneous ADRs.

4 | DISCUSSION

Skin is the most common organ affected by ADRs under pharmacological treatments, even more true when the drug targets

immunological checkpoints.[23] Using ICIs, the occurrence of adverse events, although it has not fully established, may correlate with the antitumor immune response.[5]

The two classes of immunotherapeutic agents (CTLA-4 and PD1-receptor/ligand inhibitors) recognize different molecular targets but show similar cutaneous side effects, represented by different types of maculopapular rashes with varying severity, itching, mucosal toxicity, vitiligo and lichenoid reactions, occurring in more than 30% of patients on ICI.[24-26]

Psoriasis is a chronic, immune-mediated, multifaced inflammatory skin disease having a high physical and psychosocial impact into patients' life, the estimated prevalence of which, ranging from 0.27 to 11.4% worldwide, makes the disease common.[27]

Psoriasis is also common as ADR, but its real incidence in course of ICIs has been not exactly estimated; several reports and case series have been published in the last years.[28,29]

A literature review, linked to a case presentation, was recently proposed by De Bock et al.[18] They checked a total of 35 cases of psoriasis flared during ICI therapy, now representing the largest database on this topic. According to their data, the majority of events occurred as an exacerbation of a pre-existing disease, although five reports of new onset psoriasis were reported.

The overall median time for the onset of cutaneous lesions was 31 days (mean 50.1 days), while exacerbation occurred at 28.5 days in patients with established psoriasis and at 59 days in those with de novo presentation. Management included extensive using of topical and systemic corticosteroids together with topical Vitamin D analogues/betamethasone compounds, UVB phototherapy, oral Acitretin, and Methotrexate whereas treatment with ICI was interrupted in nine patients. The authors concluded that, as psoriasis eruption is a possible ADR in course of ICIs, reliable epidemiologic data are needing for an optimal care of these patients.

In 2019, Coleman et al carried out a single-institution retrospective analysis focused on the inflammatory skin eruptions associated with ICI therapy. In their cohort a total of 98 patients (51 men, 47 women) and 103 skin eruptions were included, 17 of which (17%, eight men and nine women, mean age 67 years) having psoriasiform reactions. Only in a single case it was attributed to a CTLA-4 inhibitor, while in 12 it was caused by an anti-PD1/PD-L1 and in four by their association. The reported latency period was 5.7 months (range 0.2-28.8), with generally low severity events. With regard to the type of psoriasis, the main part was represented by classical chronic plaque or scalp psoriasis, with two inverse and two palmoplantar pustular forms; in one case also psoriatic arthritis was detected.[30]

To the best of our knowledge, our study is the first that collected ICIs-related ADR reports using the European Medicine Agency database (EudraVigilance).[31] We summarized 8213 cutaneous ADR occurring with using CTLA-4 inhibitors ipilimumab (n = 1476) and the PD-1/PD-1 ligand inhibitors nivolumab (n = 3668), pembrolizumab (n = 2532), atezolizumab (n = 341), avelumab (n = 34), and durvalumab (n = 160).

Among these events, we firstly reported a prevalence rate of 3.81% of psoriasis or psoriasiform manifestations, based on a cohort of 313 patients/cases, that represents the largest actually available in medical literature. This data is significantly different from the one presented by Coleman et al[31] (17%); however, it might be partly explained by the fact that they considered only inflammatory eruptions developed in course of ICIs. Within a sub-analysis of our data, we noted that this percentage is significantly lower in patients treated with CTLA-4 inhibitors (0.8% on ipilimumab, no available reports regarding tremelimumab), that is coherent with other studies, than in course of PD-1/PD-1 ligand inhibitors. As cutaneous eruptions have been reported in literature to be more common on CTLA-4 inhibitors than anti PD-1/PD-L1 inhibitors,[26,31] according with the extracted data we suggest that this may be not valid for psoriasis. This opposite effect should be supposed to be due to the different molecular target, but the exact mechanism has to be demonstrated.

Psoriasis and psoriasiform dermatitis are generally not serious adverse events. In our analysis, only in six cases (1.9%) immunotherapy was discontinued because of skin disease (generalized pustular dermatitis has been reported in two cases), being temporarily interrupted in 43 (13.7%). Similarly, Coleman et al. reported no discontinuation of immunotherapy, with interruption in only one out of their 17 cases (5.9%), whereas the review of literature by de Bock et al revealed discontinuation of anti-cancer treatment in two cases (5.7%) and temporary interruption in five cases (14.3%).[18,30]

Psoriasis flares were treated with either topic and systemic older drugs or newer biotechnological options, depending on the seriousness of manifestations. Because of the underlying malignant conditions, the possible causal drugs have not been always suspended whereas cyclosporine and novel biologic agents have been avoided in the majority of cases. More recently, apremilast, the PDE-4 inhibitor that has been licensed for the treatment of psoriasis and psoriatic arthritis in neoplastic patients, has been also used.

In our study, we found 145 patients (46.3%) that were treated with topical agents, including mainly steroids or combination of steroids with vitamin D analogues, and 24 (7.7%) treated with phototherapy; 10 patients (3,2%) required systemic treatment, 18 (5.7%) of which treated with systemic steroids, two with acitretin, one with cyclosporine, one with methotrexate, one with efalizumab, two with etanercept, and three with apremilast. Curiously, traditional and newer systemic antipsoriatic agents have been used only in patients on nivolumab (7) and pembrolizumab (3).

The other above mentioned two studies showed similar results.

5 | CONCLUSION

Skin toxicity represents a well-established phenomenon in course of CTLA-4 and PD-1/PDL-1 checkpoint inhibitors. Knowledge, early recognition and proper management of related conditions is mandatory in using these drugs and availability of data on these ADRs desirable.[32]

In this setting, psoriasis and psoriatic manifestations have been largely described as immune-related reactions.

As the literature is rich of single case presentations or small series, we accessed the ADR database of the European Medicines Agency to summarize the available reports and provide an overview on the topic.

Some limitations characterized our study. First of all, Eudravigilance collects all spontaneous reports on suspected ADRs sent by consumers and every kind of healthcare professionals, so, from a strictly dermatological point of view, there is a lack of useful information on the clinical features and course of the specific condition. In particular, through this data analysis is impossible to evaluate the time to onset of this ADR, the type and extent of psoriasis (in terms of PASI or BSA) and the presence of other related comorbidities, with not relevant information on concomitant therapies except for coadministered antineoplastic drugs.

This reflects the fact that the existing grading system of toxicities should not be applied to cutaneous reactions, that need several details to be appropriately assessed and managed.

In conclusion, the analysis of spontaneous ADR reports on ICIs confirmed the well-known risk associated with this drug class at the skin level, especially systemic immune-related effects.

The awareness of dermatologic toxicity to immune checkpoint blockade will become even more critical for patient care in the future, in view of the growing use of these antineoplastic agents.

AUTHOR CONTRIBUTIONS

Paola Cutroneo, Pharm.D. Ylenia Ingrasciotta, Pharm. D. and Valentina Isgrò Pharm.D. provided data extraction. Emmanuele Venanzi Rullo, M.D. and Massimiliano Berretta, M.D. assessed and checked data. Francesco Fiorica, M.D. checked the whole manuscript for content and language. Gianluca Trifirò, Pharm.D. and Claudio Guarneri, M.D. edited and supervised the paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study were derived from the following resources available in the public domain: [http://www.adrreports.eu/en/search.html].

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