Systemic Treatment of Cutaneous Adverse Events After Immune Checkpoint Inhibitor Therapy: A Review

Alexandria M. Brown, BSA,* Wylie Masterson, BSA,† Jonathan Lo, BS,* and Anisha B. Patel, MD†‡

As treatment with immune checkpoint inhibitors (CPIs) for cancer increases, so has the incidence of immune-related cutaneous adverse events (irCAEs). These toxicities can significantly impact quality of life and may be dose-limiting. Current guidelines for irCAEs offer only corticosteroids or CPI discontinuation. Evidence supports biologic immunomodulatory therapies when corticosteroids fail or need avoidance. A review of literature from 2010 to 2020 yielded 45 articles, resulting in 185 irCAEs, including bullous pemphigoid–like eruption (n = 55), psoriasis/psoriasiform dermatitis (n = 41), and maculopapular rash (n = 31). Treatments included immunomodulators, intravenous immunoglobulin, aprepitant, acitretin, tetracyclines, and biologic agents. Overall, 92.3% of patients saw improvement or resolution of their rash. Bullous pemphigoid–like eruptions were treated with a tetracycline +/− niacinamide (94.7% success [18/19]), omalizumab (100% success [7/7]), and rituximab (100% success [10/10]). Although prospective research is required, this review provides a comprehensive list of successful, non-corticosteroid treatment options for irCAEs to improve compliance with lifesaving cancer therapy.

Immune checkpoint inhibitors (CPIs) represent a relatively new class of immunotherapy that has revolutionized the management of cancer patients. Because CPIs generally exert their antitumor effects through upregulation of the host immune response, this can consequently lead to unwanted, off-target immune-related adverse events.[1] Often the first and most common immune-related adverse event seen with CPIs is a cutaneous adverse event (irCAE).[2,3] They occur in up to 45% of patients on cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitors and up to 34% on programmed cell death protein 1 (PD-1)/PD-1 ligand (PD-L1) inhibitors.[4] Although only 1% to 3% are reported as grade 3 or 4 events, they can have a significant impact on quality of life.[5,6]

Common irCAEs seen with CPIs include pruritus, morbilliform exanthem, psoriasiform eruptions, lichenoid reactions, and vitiligo-like depigmentation.[7,8] Because of the novelty of CPIs and the low incidence of high-grade events, there are a lack of data on best practices. There have been few prospective trials to guide treatment of irCAEs; so much of our knowledge is based on clinical experience and anecdotal reports in the literature.

*From the *Baylor College of Medicine, School of Medicine, Houston, TX; †McGovern Medical School, University of Texas Health Science Center at Houston; and ‡Department of Dermatology, The University of Texas MD Anderson Cancer Center, Houston.*

Address reprint requests to Anisha B. Patel, MD, Department of Dermatology, The University of Texas MD Anderson Cancer Center, Unit 1452, 1515 Holcombe Blvd, Houston, TX 77030. E-mail: apatel11@mdanderson.org.

The authors have no funding or conflicts of interest to declare.

DOI: 10.1097/DER.0000000000000776

The American Society of Clinical Oncology has proposed a modified version of the Common Terminology Criteria for Adverse Events to guide management of general skin toxicities based on severity grading. Their grading focuses on symptoms and quality of life rather than body surface area involvement, which appears to better characterize the severity as small body surface area involvement can still be dose limiting.[8,9] Immune-related cutaneous adverse events typically resolve within 6 to 12 weeks of corticosteroid therapy, and most of the current treatment guidelines focus on topical or systemic corticosteroid administration. Systemic steroids are not always a viable option if the patient needs to continue CPI therapy and has a prolonged course of his/her irCAE.

There is concern that the early use of corticosteroids during CPI therapy may impair immunotherapy efficacy, negatively affecting the rate or quality of tumor response and survival.[10–16] This, however, is an area of debate as other studies report no such effects for those receiving corticosteroids or other immunosuppressive therapies.[4,14,17] Because the goal of immune CPI therapy is to illicit a targeted immune response toward the malignancy, oncologists would theoretically want to avoid a state of generalized immunosuppression produced by systemic corticosteroids and would favor targeted immunomodulation toward the rash-inducing pathogenic mechanism.

Further, when oncologists are faced with grades 3 to 4 corticosteroid-refractory dermatologic toxicity, current guidelines only suggest an urgent dermatology referral and cessation of immunotherapy.[9,18] This review intends to explore the reported non-corticosteroid systemic therapies for irCAEs with descriptions of patient scenarios, treatment regimens, and adverse effect data.

An area of significant interest is the impact of CPI discontinuation and systemic irCAE therapies on tumor response and survival. One study suggested that roughly 25% of patients on CPIs experiencing irCAEs required temporary or permanent discontinuation of immunotherapy.[19] This is more commonly seen with severe dermatologic toxicities, highlighting the importance of early identification and intervention as this has been shown to reduce both their severity and duration.[6]

A growing body of clinical evidence has suggested the use of targeted biologic and immunomodulatory therapies for certain corticosteroid-refractory irCAEs.[20] Because the use of biologic agents for irCAEs is still an area of active research, little is known about their implications on tumor progression. Although the use of tumor necrosis factor α inhibitors is not seen in this review, cases reporting a possible associated risk of leukemia development are examples of the potential unintended risks associated with biologic agents.[21,22] To note, one case reported a loss of tumor response following interleukin 17 (IL-17) blockade treatment for immune-related skin and gastrointestinal toxicities associated with pembrolizumab.[23] However, many biologic agents, such as omalizumab, have not demonstrated an increased risk of malignancy to date.[24] In summary, it is difficult to assign associations and causality with single case reports. Tumor necrosis factor α inhibitors have the most evidence associated with potential malignancy, and based on our review, dermatologists seem to be respectful of that and choose more targeted biologic agents. Because there are few data on their safety or efficacy in patients on CPIs, more research is required to determine their potential risks.

A thorough compilation and review is presented to guide clinicians in their decision-making process until we have more robust prospective data. As the uses for CPIs continue to grow, dermatologists will be expected to recognize and offer nuanced treatment options for patients experiencing irCAEs.

METHODS

Design and Search Strategy

We conducted a search of the literature to identify case series, case reports, reviews, and clinical trials of CPI-induced irCAEs treated with systemic agents. Using PubMed as our search engine, the keywords "immune checkpoint inhibitors," "cutaneous adverse events," "skin manifestations," and "treatment" and other similar terms were used. Search strings were created with Boolean operators. The database was searched for articles published on or before October 18, 2020. Articles were first screened by title and abstract for relevance. The final screen reviewed full-text articles. Selected articles were subsequently hand searched for additional relevant references.

Eligibility Criteria

Our selection criteria included all reports that are as follows: (1) involved patients being treated with CPIs for a malignancy; (2) reported an irCAE, with or without clinical severity grading; (3) the irCAE was treated with steroid-sparing agents; and (4) were published in the English language. The systemic treatments included were tumor necrosis factor α inhibitors, anti–IL-17 biologic therapy, anti–IL-23 and related cytokines, efalizumab, rituximab, alefacept, acitretin, apremilast, thalidomide, methotrexate, sulfasalazine, intravenous immunoglobulin (IVIG), hydroxychloroquine, doxycycline, minocycline, tocilizumab, aprepitant, niacinamide, omalizumab, dapsone, mycophenolate mofetil, and cyclosporine. Studies were excluded if systemic treatment of irCAEs was limited to steroids and/or antihistamines.

Data Extraction

Data extraction included study type, total number of patients with CPI-induced irCAEs, patient age, sex, and ethnicity, primary malignancy treated, CPI used to treat malignancy, number and types of irCAEs, systemic treatment used for irCAE, time from CPI to rash presentation, use of systemic corticosteroids, and time from treatment of rash to resolution where available.

Data Analysis

Qualitative and descriptive analyses were performed. Immune-related cutaneous adverse event treatment was deemed "successful" if resolution, improvement, or control of the irCAE was noted. The aggregate data from the 2 review studies were included when possible.[20,25]

RESULTS

Overall, our study included 45 articles with a total of 457 patients (259 men, 197 women, and 1 unspecified). Most articles were case reports and case series with level 4 or level 5 evidence. Within those patients, 185 patients with irCAEs (40 men, 27 women, and 118 unspecified) met eligibility criteria for analysis. The median age was 67 years (range, 29–90 years). Primary malignancies included both solid and hematological malignancies (Table 1). In the publications that specified therapy, the CPIs used were anti–PD-1 (nivolumab, pembrolizumab), anti–PD-L1 (atezolizumab, durvalumab), anti–CTLA-4 (ipilimumab), and combination therapy (ipilimumab + anti–PD-1) (Table 2). Two review articles did not provide stratified data for individual patients and did not specify the individual treatments. Their data are included in Table 2 and Table 3 under unspecified therapy.

The most common malignancies were non–small cell lung carcinoma (n = 27 [40%]) and melanoma (n = 27 [40%]). Roughly 42% (63/151, with reported data) of patients experienced an interruption or discontinuation in CPI therapy because of the irCAE. The average time to irCAE onset was 158 days (22.6 weeks). Common irCAEs requiring systemic treatment included bullous pemphigoid (BP)–like eruption (n = 55), psoriasis/psoriasiform dermatitis (n = 41), and maculopapular rash (n = 31). All included irCAEs and their treatments are summarized in Table 3.[20,23–65]

Common non-corticosteroid systemic treatments included antipruritics (eg, aprepitant), immunomodulators (eg, hydroxychloroquine, quinacrine, methotrexate, cyclosporine), IVIG, acitretin, antibiotics

TABLE 1. Patients on Systemic Therapy for irCAEs (n = 185)

Age,* y	
Median age	66.5
Range	29–90
Sex*	
Male	40
Female	27
Primary cancer type,* n	
Melanoma	27
Non–small cell lung cancer (adenocarcinoma, large, and squamous cell)	27
GI (colon, esophageal, hepatoma)	3
Ovarian carcinoma (serous and clear cell)	2
Renal cell carcinoma	2
Small cell lung carcinoma	2
Urothelial cell carcinoma	2
Acute myeloid leukemia	1
Merkel cell carcinoma	1
Sarcoma	1

GI, gastrointestinal; irCAEs, immune-related cutaneous adverse events.

**Data not available for all patients.*

(eg, tetracycline + niacinamide, doxycycline, and dapsone), and biologic agents (eg, tocilizumab, secukinumab, omalizumab). Most patients saw improvement or resolution of their irCAE with nonsteroidal systemic therapies (92.3% [156/169]).

The most common successful treatment regimens for BP-like rashes include a tetracycline +/− niacinamide (94.7% success [18/19]), omalizumab (100% success [7/7]), or rituximab (100% success [10/10]). Of the patients with psoriasiform dermatitis, commonly reported successful treatments include acitretin, secukinumab, and methotrexate. Treatment of other severe irCAEs (eg, erythema multiforme major, Stevens-Johnson syndrome, and toxic epidermal necrolysis [TEN]) often incorporated IVIG (3 of 6 patients) in conjunction with systemic corticosteroids. Hydroxychloroquine was successfully used in 3 of 3 patients with leukocytoclastic vasculitis and 3 of 3 patients with lupus-like reactions.

Thirteen irCAEs required 1 to 2 trials with different biologic agents and/or immunomodulating agents before finding a successful rash treatment. These unsuccessful treatments included acitretin for psoriasiform rash, a tetracycline with or without niacinamide, and/or dapsone for BP-like eruptions,[53,55,58,64] trimethoprim-sulfamethoxazole, tazobactam with piperacillin, granulocyte colony-stimulating factor, and blood transfusion for EM major,[41] IV acyclovir and vancomycin for EM major,[37] IV vancomycin for TEN,[65] and infliximab and mycophenolate mofetil for pemphigus lesions.[51]

The data recorded for "time to irCAE resolution" were widely variable, and for many reports, these data were not included. Three patients' CPI dosing frequency was reduced after rash onset (data not shown). Four patients discontinued CPI before the rash presented. One stratified patient did not have a rash outcome reported.

DISCUSSION

Current treatment guidelines for moderate to severe irCAEs focus on high-dose systemic corticosteroids and offer few alternatives for when they fail. Corticosteroid failure, long-term sequelae of corticosteroid use, and CPI cessation due to irCAE severity have led to increased interest in the use of nonsteroidal therapy for irCAE management. There are many case reports of irCAEs being treated with nonsteroidal systemic treatments, but to our knowledge, there are no comprehensive reviews of these data. The results of this study demonstrate the wide variety of corticosteroid-refractory irCAEs and provide a thorough compilation of the agents successfully and safely used to treat them in the literature.

Interestingly, patients who develop irCAEs with certain cancer types likely have significantly longer progression-free intervals than those who do not,[19] emphasizing the importance of developing treatment strategies to manage these toxicities. As CPI use continues

TABLE 2. Rash-Inducing Checkpoint Inhibitor Data

CPI Therapy	Total, n	CPI Dose Unaffected, n	CPI Dose Discontinued, n	CPI Interrupted, n	CPI Dose Modified, n	CPI Dose Status Unspecified, n	Days to irCAE, Average (Range)	Time to irCAE Not Specified, n
Nivolumab	32	7	18	4	1	2	137 (14–609)	2
Pembrolizumab	27	3	16	2	2	4	171 (21–609)	1
Ipilimumab + anti–PD-1 (combo)	4	0	1	2	0	1	305 (62–364)	0
Atezolizumab	2	0	1	1	0	0	281 (15–546)	0
Ipilimumab	2	0	0	2	0	0	7	0
Durvalumab	1	0	1	0	0	0	152	0
Unspecified systemic therapy*	117	35	1	1	0	80	Unknown	117

**Unspecified systemic therapies include CTLA-4, PD-1/PD-L1, or combination therapy.*

CPI, checkpoint inhibitor; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; irCAE, immune-related cutaneous adverse event; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand.

TABLE 3. Systemic Treatment of irCAEs

irCAE Rash Type	No. Patients	Systemic Treatment	No. Patients	Corticosteroid Use (Conc/Prior/ Unk/None), No. Patients	CPI Impact (Stop/Intr/ None/Unk), No. Patients	Improved irCAE,* No. Patients (%)	Tumor Response (CR, PR/Stable/ PD/Unk), No. Patients
BP-like lesions	55	Doxycycline + niacinamide	10	4/2/2/2	5/3/0/2	9 (90)	0/0/5/5
		Doxycycline	8	3/1/2/3	5/0/0/3	6 (100)	2/3/1/2
		Rituximab	8	2/7/0/3	5/0/0/3	8 (100)	3/0/1/2
		Omalizumab	6	2/3/2/0	1/2/1/2	6 (100)	1/1/2/2
		Acitretin	2	1/1/0/1	1/0/0/1	2 (100)	0/1/1/0
		MTX	3	2/1/1/0	1/0/0/2	3 (100)	2/0/1/0
		Dapsone	3	2/1/1/0	1/0/0/2	2 (67)	0/1/0/2
		Minocycline + niacinamide	1	1/1/0/0	1/0/0/0	1 (100)	0/0/0/1
		Mycophenolate mofetil	1	0/0/0/1	1/0/0/0	1 (100)	0/0/0/1
		IVIG + rituximab	1	1/1/0/0	1/0/0/0	1 (100)	0/0/1/0
		Omalizumab + MTX	1	1/0/0/0	1/0/0/0	1 (100)	0/1/0/0
		PEX + rituximab	1	1/1/0/0	1/0/0/0	1 (100)	0/0/0/1
		Unspecified immunomodulators	10	0/0/10/0	0/0/0/10	Unk	0/0/0/10
Psoriasiform	41	Acitretin	7	0/0/2/5	1/0/4/2	4 (80)†	0/0/0/7
		Secukinumab	3	1/1/0/2	1/1/0/1	3 (100)	1/1/1/0
		MTX	3	2/0/1/0	0/1/1/1	2 (100)†	0/0/0/3
		Apremilast	1	0/0/0/1	0/0/1/0	1 (100)	0/0/0/1
		Doxycycline	1	1/1/0/0	1/0/0/0	–	0/0/0/1
		Etoposide	1	0/1/0/0	1/0/0/0	1 (100)	0/0/0/1
		Guselkumab	1	0/1/0/0	0/0/0/1	1 (100)	0/0/0/1
		Ustekinumab	1	0/1/0/0	0/0/0/1	1 (100)	0/0/0/1
		Unspecified immunomodulators	6	0/0/6/0	0/0/0/6	Unk	0/0/0/6
		Unspecified systemic treatment‡	17	0/0/4/0	0/1/16/0	16 (94)	0/0/0/17
Morbilliform/ maculopapular	31	Aprepitant	1	1/1/0/0	1/0/0/0	1 (100)	0/0/1/0
		Tocilizumab	1	0/0/0/1	1/0/0/0	1 (100)	0/0/0/1
		Unspecified immunomodulators	29	Unknown	0/0/0/29	20 (69)	0/0/0/29
Lichenoid	9	Cyclosporine	1	1/1/0/0	1/0/0/0	1 (100)	1/0/0/0
		Acitretin	1	Unknown	0/0/0/1	Unk	0/0/0/1
		Doxycycline	1	Unknown	0/0/0/1	Unk	0/0/0/1
		Unspecified immunomodulators	6	Unknown	0/0/0/6	6 (100)	0/0/0/6
EM/SJS/TEN	5	IVIG	2	2/2/0/0	0/2/0/0	2 (100)	0/0/0/2
		Minocycline + valacyclovir	1	1/0/0/0	1/0/0/0	1 (100)	0/0/0/1
		IVIG + cyclosporine	1	1/1/0/0	1/0/0/0	1 (100)	0/0/1/0
		Infliximab	1	1/0/0/0	1/0/0/0	1 (100)	0/0/0/1
CTD: lupus	3	Hydroxychloroquine	2	0/0/0/2	1/0/1/0	2 (100)	0/0/1/1
		Hydroxychloroquine + quinacrine	1	1/1/0/0	0/0/0/1	1 (100)	0/0/0/1
Leukocytoclastic vasculitis	3	Hydroxychloroquine	2	2/0/0/0	0/0/0/2	2 (100)	0/2/0/0
		Hydroxychloroquine + MTX	1	1/0/0/0	0/0/0/1	1 (100)	0/1/0/0

(Continued on next page)

TABLE 3. *(Continued)*

irCAE Rash Type	No. Patients	Systemic Treatment	No. Patients	Corticosteroid Use (Conc/Prior/ Unk/None), No. Patients	CPI Impact (Stop/Intr/ None/Unk), No. Patients	Improved irCAE,* No. Patients (%)	Tumor Response (CR, PR/Stable/ PD/Unk), No. Patients
CTD:	2	IVIG	1	1/1/0/0	1/0/0/0	1 (100)	0/1/0/0
dermatomyositis		MTX, IVIG, hydroxychloroquine	1	1/0/0/0	0/0/1/0	1 (100)	0/0/1/0
Eczematous	2	Dupilumab	2	0/2/0/0	0/0/0/2	2 (100)	0/0/0/2
Scleroderma	2	Hydroxychloroquine	1	1/0/0/0	1/0/0/0	1 (100)	0/0/0/1
		IVIG + mycophenolate mofetil	1	1/1/0/0	1/0/0/0	1 (100)	1/0/0/0
Erythema nodosum	1	Hydroxychloroquine	1	1/0/0/0	1/0/0/0	1 (100)	1/0/0/0
Erythroderma	1	Acitretin	1	0/0/0/1	0/0/1/0	1 (100)	0/0/0/1
Mucositis	1	Tocilizumab	1	1/1/0/0	1/0/0/0	1 (100)	1/0/0/0
Pemphigus	1	MTX	1	1/1/0/0	1/0/0/0	1 (100)	1/0/0/0
PRP-like	1	Acitretin	1	0/0/0/1	1/0/0/0	1 (100)	0/0/0/1
Other unspecified	27	Unspecified immunomodulators	7	Unknown	0/0/0/7	4 (57)	0/0/0/7
		Unspecified systemic treatment‡	20	Unk/unk/2/unk	1/0/19/0	16 (80)	0/0/0/20

**Improvement includes resolution of rash, controlled rash, and improvement of rash.*

†Two psoriasiform treated with acitretin and 1 psoriasiform rash treated with methotrexate did not specify the outcome of systemic therapy; unspecified fate of CPI and unspecified malignancy outcomes were excluded from the table.

‡Systemic therapy not specified.

conc., concurrent; CPI, checkpoint inhibitor; CR, complete response; CTD, connective tissue disease; EM, erythema multiforme; Intr, interruption; irCAE, immune-related cutaneous adverse event; IVIG, intravenous immunoglobulin; MTX, methotrexate; PD, progression of disease; PEX, plasma exchange; PR, partial response; PRP, pityriasis rubra pilaris; SJS, Stevens-Johnson syndrome; TEN; toxic epidermal necrolysis; unk, unknown.

to expand, the number of severe irCAEs requiring treatment will also continue to rise.

Although BP is a relatively rare irCAE, it is significant in its need for higher-level management. Of the 185 irCAEs analyzed, 55 (29.73%) were BP. Also overrepresented are EM/SJS/TEN and connective tissue disease. Morbilliform drug eruption, psoriasis, and lichenoid dermatitis are seen frequently with anti–PD-1/PD-L1 therapy and would be expected to have a higher incidence of severe presentations.

Data are difficult to analyze, because patients who have irCAEs overall may have increased tumor response, which has been shown in multiple studies for melanoma patients.[19,66–68] This group then is naturally skewed to having better outcomes, and evaluating the effect of additional systemic therapies on these patients' tumor response must be done cautiously. Analysis between the treatment groups is not possible because all had high success rates. This study does, however, highlight the wide range of potential options for treatment of severe-grade reactions and their relative safety and anecdotal efficacy.

There is a delicate balance between the treatment of irCAEs and the desire to maintain the efficacy of the CPI. Many of the nonsteroidal immunomodulating treatment options, such as biologic agents, target a specific pathway, IL, or antibody and offer a more targeted inhibition of inflammatory cells when compared with the more generalized immunosuppression elicited by corticosteroids. Therefore, in theory, these agents should not interact with the PD-1/PD-L1 or CTLA-4 interactions targeted by immune CPIs and have the potential to mitigate irCAEs without affecting the antitumor efficacy of CPIs. For example, the IL-17 monoclonal antibody, secukinumab, has been hypothesized to play both positive and negative roles in the antitumor effects of CPIs. Although some studies in mice suggest that T_H17 cells secrete proinflammatory cytokines that can promote tumor growth and metastasis,[69] other studies have shown that IL-17 and T_H17 cells enhance tumor surveillance.[70–72] These contradictory studies highlight the need for more research to confirm the safety of IL-17 blockade in patients on CPIs. In another example, recent studies have suggested a possible therapeutic value of anti-CD20 therapy in melanoma patients with subpopulations of CD20-positive "tumor stem cells."[73] Therefore, rituximab, which has successfully been used to treat BP irCAEs, may have potential antitumor benefits in this population. One could hypothesize that agents, such as methotrexate, with both anti-inflammatory and anticancer properties, could positively affect the antitumor response when used to treat irCAEs. This phenomenon has been seen in patients with a long-term history of rheumatoid arthritis treated with methotrexate who develop breast cancer that histologically mimics the histopathological changes seen after neoadjuvant chemotherapy, thus suggesting methotrexate's possible concurrent chemotherapeutic role.[74–76]

We are learning more about the regulation of tumor response and toxicities, but it is still unclear whether immunomodulators have a detrimental effect, and to what capacity, on the CPI and

tumor response. It is reassuring that nonimmunomodulating systemic therapies for BP, including tetracyclines +/− niacinamide, acitretin, and dapsone, were efficacious. Acitretin had efficacy for BP, psoriasis, lichenoid dermatitis, erythroderma, and pityriasis rubra pilaris–like eruption, making it a good first-line systemic therapy based on its nonimmunomodulating mechanism.

A number of biologic agents were used in small numbers with excellent efficacy. Twenty-seven patients were treated with biologic agents (2 in combination with methotrexate or plasma exchange and 10 in combination with oral steroids), with 100% of patients achieving significant improvement or resolution. Of these patients, 13 (50%) had discontinuation of the CPI with rash onset, 3 were delayed and successfully rechallenged, and 1 (BP patient treated with omalizumab) had no dose impact. Nine patients had a stable or responsive primary tumor, and 5 had progressive malignancy. No major adverse effects were reported to the biologic agents. These are obviously limited data, but there is an argument for initiating biologic agents earlier in severe irCAE courses to decrease CPI impact and keep patients on effective therapy.

Fourteen patients were treated with an unspecified immunomodulator either in monotherapy or combination therapy (methotrexate, mycophenolate mofetil, etoposide, cyclosporine). Thirteen patients had improvement of rash, and one is unknown. Six patients had a stable or responsive primary tumor, and 3 had progression of disease.

Nine patients were treated with hydroxychloroquine, all for dermatologic-rheumatologic disease and all successfully. Four patients had stable or responsive primary tumors, with 2 having progressive disease.

Many of the nonsteroidal systemic treatment options for irCAEs are thought to target a specific pathway or interaction involved in the rash pathogenesis. For example, omalizumab is a humanized anti–immunoglobulin E (IgE) antibody that lowers free IgE levels and prevents mast cell activation. Although omalizumab is Food and Drug Administration–approved to treat asthma and chronic urticaria, recent studies have found high levels of IgE autoantibodies to be associated with severe presentations of BP, thus making omalizumab a possible effective treatment option for BP-like irCAEs.[77,78] In addition, it appears that drug-induced psoriasis is mediated by the same markers as autoimmune psoriasis so the T_H17 pathway can be similarly targeted. This notion has been proven by the high efficacy of these drugs in drug-induced psoriasis.[23,50,56,79]

Cost is also an issue. Checkpoint inhibitors represent expensive therapy, and the host of monitoring scans and laboratory work associated with this therapy is significant as well. An additional biologic can be difficult to get if not for a Food and Drug Administration–approved indication and places a significant financial burden on the patient and medical system. Acitretin and hydroxychloroquine are old, cheap, well-studied medications that can be used successfully in appropriate situations. Biologic agents do play a role in treating severe irCAEs, particularly when patients have no further treatment options, and developing predictive models about the time course and characteristics of those patients requiring the drug will help us target our treatment to those with the greatest potential benefit from biologic agents and hopefully also initiate early treatment.

Limitations of this study include selection bias as researchers are more inclined to publish successful cases of irCAE treatment. We realize that steroid-refractory rashes represent a small subset of the possible irCAEs, limiting our sample size and external validity, but it ends up being an important subset because CPI therapy is often impacted. The 2 review articles included in this article did not delineate individual patients treated with systemic therapy with their treatment outcome; therefore, aggregate data were used.

CONCLUSIONS

Compared with corticosteroids, biologic agents and other nonimmunomodulating therapies use a more targeted inhibition of the inflammatory response and can therefore mitigate irCAEs without overtly affecting the antitumor efficacy of CPIs. Non-corticosteroid systemic treatments should be considered in patients with irCAEs threatening cessation of their CPI therapy.

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