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The importance of considering skin diseases from a temporal perspective: Special emphasis on the effects of corticosteroids and virally induced diseases

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Abstract

The efficacy and safety of medical therapies assessed on the basis of short-term outcomes are often considered to inform the long-term outcomes. Even in corticosteroid therapy, either systemic or topical, which is most frequently used as a first-line therapy to control inflammation, few studies have reported the risk/benefit ratio for long-term outcomes. Thus, a temporal perspective should be added to our conventional understanding of the effectiveness of medical therapies. In this review, we initially describe the importance of considering the efficacy of corticosteroid therapy based not only on short-term outcomes, but also on long-term outcomes of a certain type of severe drug eruption, drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DiHS/DRESS). Our view is exemplified by our recent analysis of previously reported cases of DiHS/DRESS, revealing that aggressive treatment such as pulsed corticosteroids and intravenous immunoglobulin, although beneficial in the short term, paradoxically has deleterious effects such as autoimmune sequelae in the long term. Thus, measuring the therapeutic efficacy from only a short-term perspective is insufficient and follow-up examination of these patients for at least three years is required even after complete resolution is observed. Various cutaneous diseases refractory to conventional therapies that occur after resolution of herpes zoster also require a temporal perspective to understand how cutaneous diseases develop at a certain site. We describe the clinical usefulness of considering the dual actions of corticosteroids, antiinflammatory, and immunostimulatory, depending on the situations in which they are used.

1 | INTRODUCTION

Corticosteroids, either topical or systemic, are most frequently used as a first-line therapy to control inflammation in patients with autoimmune diseases and cutaneous inflammatory diseases. The safety of corticosteroid use over long periods, however, is always a concern, although previous long-term, controlled studies suggest that

Abbreviations: autoAb, autoantibody; DiHS/DRESS, drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms; HZ, herpes zoster; IMQ, imiquimod; IRIS, immune reconstitution inflammatory syndrome.

long-term adverse effects, such as osteonecrosis, are uncommon when the corticosteroid dosage is low.[1,2] Thus, it is important to investigate whether the efficacy and safety in the short term necessarily assure the safety and efficacy in the long term. Even in corticosteroid therapy, however, few studies have demonstrated the risk/benefit ratio in the long term; an excellent risk-benefit ratio of a certain therapy in the short term may not be necessarily favorable in the long term. It is also difficult to evaluate the effectiveness of medical therapy because of the effect of the disease duration before therapy is started; if treated early, many patients might have a life expectancy similar to that in a healthy control population, but if treatment is delayed, patients with late-stage disease might have a significantly greater risk of morbidity and mortality. Thus, a temporal perspective should be added to our conventional understanding of the effectiveness of medical therapy.

In addition, considering skin diseases as dynamic processes in which phenotypic manifestations evolve in a continuous manner rather than as a distinct disease onset is important in terms of understanding the pathogenesis or management. Indeed, careful follow-up of patients for years may reveal the transformation of an immature form of disease into a more classic or typical form of disease; typical examples of such transitions are often reported and include conversion from granuloma annulare to sarcoidosis and from discoid lupus erythematosus to systemic lupus erythematosus. In this review, we focus on the importance of considering skin disease as a continuous spectrum rather than as a binary process (ie, present or absent). In support of this possibility, we recently demonstrated that a variety of inflammatory diseases such as lichen planus (LP) and lichen amyloidosis (LA) develops in previously healed herpes zoster (HZ) lesions (manuscript submitted).[3] [NOTE: Rather than "manuscript submitted," please report the "authors name(s), personal communication."] We further describe how autoimmune sequelae or autoantibodies (autoAbs) arise long after the clinical resolution of severe drug eruptions and then trigger events that drive the disease process forward.

2 | AUTOIMMUNE SEQUELAE IN SEVERE DRUG ERUPTIONS

Severe drug eruptions encompass two distinct clinical entities, the most common being drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS). Another is Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). On the basis of clinical comparisons as well as immunologic studies of the two diseases, these two forms of severe drug eruptions likely have distinct pathogenic mechanisms,[4,5] although some of the causative drugs are common. DiHS/DRESS is characterized by sequential reactivations of herpesviruses, probably due to functional defects in regulatory T cells (Tregs).[6] Several autoimmune diseases and the generation of autoAbs concurrently or sequentially occur as sequelae of DiHS/DRESS.[7–9] Inflammation and subsequent damage to the skin and liver in patients with DiHS/DRESS are thought to lead to autoAbs generation and the onset of autoimmune disease.[9] Treatment is therefore aimed at suppressing the inflammation early and preventing the development of tissue destruction. Although systemic corticosteroids are accepted as the gold standard treatment for ameliorating the clinical symptoms of DiHS/DRESS, it is unclear whether aggressive therapies such as pulsed corticosteroids or high doses of intravenous immunoglobulin (IVIG) would be more effective than the usual dosage of prednisolone (40-60 mg/d) for reducing symptoms and damage. Because autoimmune sequelae such as autoimmune thyroiditis, type 1 diabetes mellitus, and lupus erythematosus[10–12] may develop long after clinical resolution of DiHS/DRESS, the effect of systemic corticosteroid treatment for DiHS/DRESS should be evaluated not only for short-term outcomes, but also for long-term outcomes. In this regard, we investigated whether systemic corticosteroid treatment during the acute stage could be efficacious for both short-term and long-term outcomes. In our retrospective analysis,[13] patients with DiHS/DRESS were divided into two groups depending on the use of systemic corticosteroids during the first six-month period. During this period, various clinical symptoms due to reactivation of herpesviruses and other bacterial infections occurred more frequently in the corticosteroid-treated group than in the noncorticosteroid-treated group; in the corticosteroid-treated group, the findings were thought to relate to the reduction or withdrawal of corticosteroids. Flare-ups of the original symptoms of the disease also occurred more frequently in the corticosteroid-treated group upon reduction or withdrawal of the corticosteroid dose. Marked deterioration of various clinical symptoms is observed following accidental discontinuation or rapid tapering of corticosteroids.[13,14] We recommend that corticosteroids started at a dose of 40-60 mg/d be tapered over a period of six to eight weeks to prevent the relapse of various clinical symptoms and therefore continued for two to three months. Corticosteroid doses should be reduced gradually (10 mg/d for about two weeks), even upon clinical resolution of the disease manifestations. A reasonable explanation for this is that DiHS/DRESS represents another manifestation of immune reconstitution inflammatory syndrome (IRIS), which is observed with a broad-spectrum of immunosuppressive therapy-related opportunistic infectious diseases.[14,15] According to the concept of IRIS, reactivation of various latent viruses might occur upon the rapid recovery of immune responses against previously unrecognized viruses during the immunosuppressed state, even before the onset of DiHS/DRESS. Therefore, for better management of DiHS/DRESS, relieving the inflammatory symptoms and signs of immune recovery by immunosuppressive agents should be balanced with antimicrobial therapies aimed at reducing the amplitude and duration of the tissue burden of preexisting pathogens.[15] Thus, the use of systemic corticosteroids should also be recognized as an important factor that increases the risk of disease progression to the full manifestation of IRIS upon discontinuation or reduction of the dose. This would account for the frequent viral reactivations or bacterial infections in the first 6-month period of DiHS/DRESS in the corticosteroid-treated group.[13] These results suggest that early intervention with systemic corticosteroids does not necessarily lead to better

long-term outcomes, contrary to our initial expectation. In this case, would administration of pulsed corticosteroids or IVIG, which is effective for treating SJS/TEN, also be effective for treating DiHS/DRESS? We are concerned that these aggressive therapies may have adverse consequences in either the short or long term, because these therapies are intrinsically associated with a process that requires either rapid or great reduction or discontinuation of the prednisolone immediately after therapy.

In this regard, we recently searched for published DiHS/DRESS cases with autoimmune sequelae. Most, if not all, reported cases with autoimmune sequelae had clinical features consistent with type III polyglandular autoimmune syndrome, which is characterized by the coexistence of at least two glandular autoimmune diseases.[16] Most importantly, pulsed corticosteroids or IVIG was used to treat DiHS/DRESS during the acute stage in four of the five reported DiHS/DRESS cases that eventually developed type III polyglandular autoimmune syndrome. Although the current literature recommends aggressive treatment with systemic corticosteroids followed by a slow taper or IVIG therapy, autoimmune sequelae developed more than six months after successful resolution of the initial clinical symptoms with these therapies in the previously reported cases.[7,10,17] These results indicate that treatment outcomes in DiHS/DRESS should be assessed with long-term follow-ups of at least six months after clinical resolution.

In contrast to the short-term outcome, in which noncorticosteroid treatment was thought to be more beneficial than corticosteroid treatment, our data on the effect of systemic corticosteroids on the long-term outcomes of DiHS/DRESS suggest the opposite of what would be expected from the results of the short-term outcomes. Autoimmune disease developed more frequently in the noncorticosteroid-treated group than in the corticosteroid-treated group.[9] Considering that inflammation associated with severe tissue damage is thought to be an underlying or preceding event for the subsequent development of autoimmune diseases, the severe tissue damage associated with Treg dysfunction observed in the acute to resolution stages (days 11-36) of DiHS/DRESS may increase the risk for developing autoimmune disease. We then considered whether the generation of autoAbs against plakin family protein was related to tissue damage in the acute stage and if the subsequent generation of autoAbs could be prevented by the use of systemic corticosteroids. We found that severe liver damage during the acute stage of DiHS/DRESS was associated with subsequent generation of autoAbs to the plakin family and that the autoAb generation could be prevented by administering systemic corticosteroids during the acute stage. In view of our unpublished observation that Treg function gradually decreased during the subacute stage (days 11-36) after the peak of severe liver damage, the severe liver damage and defective Treg function must have occurred sequentially and not concomitantly to optimize the subsequent generation of autoAbs. It is possible that dysfunctional Tregs unable to limit the proliferation of autoreactive effector T and B cells would allow for the generation of autoAbs, leading to the development of autoimmune disease. Interestingly, the expanded numbers of Tregs in the acute stage rapidly contracted in association with rapid immune recovery during the subacute stage (days 11-36; Figure 1) in the noncorticosteroid - treated group whereas the decrease was not so remarkable in the corticosteroid-treated group. It is therefore likely that systemic corticosteroids administered during the subacute stage attenuated the rapid immune recovery, thereby preventing the progression to autoimmune disease. If so, a "golden window" for beneficial long-term outcomes may exist in DiHS/DRESS patients; if not treated with sufficient, but not too high, doses of systemic corticosteroids during the subacute stage, irreversible liver damage and rapid immune recovery, both of which could result in the subsequent generation of autoAbs, may ensue. Thus, there may be a time-dependent "golden window" (subacute stage) where corticosteroid intervention is useful before irreversible tissue damage and rapid immune recovery occur. Treatment with systemic corticosteroids, if considered, should therefore be initiated to ameliorate a rapid immune recovery and tissue damage during the subacute stage; nevertheless, pulsed corticosteroids or IVIG should not be used during this stage. At least, during the subacute stage of DiHS/DRESS, corticosteroids should not be discontinued if they are initiated at the acute stage to prevent progression to the development of autoimmune sequelae. In support of this view, the development of autoimmune diseases and generation of autoAbs were significantly decreased in the corticosteroid-treated group compared with the noncorticosteroid-treated group.[9,13] These findings highlight the importance of considering the efficacy of treatment based not only on the short-term outcomes, but also on the long-term outcomes. Another issue is that these patients receive inpatient or outpatient hospital care for the acute to subacute stage of DiHS/DRESS but will be subsequently treated by their general practitioner who has little information on the subsequent development of autoimmune disease after resolution of the acute inflammation in DiHS/DRESS. More importantly, physicians who treat DiHS/DRESS patients in the acute ~ subacute stage may lack sufficient information as to whether the treatment options they select during the early period will be beneficial for the long-term outcome as well the short-term outcome. The deleterious effects of aggressive treatment such as pulsed corticosteroids on the long-term outcome in some patients have received little attention. As a result, dogma established by these physicians emphasizes the efficiency of aggressive therapies such as pulsed corticosteroids solely on the basis of the short-term outcome. These physicians are believed, by themselves as well as other physicians, to be experts despite lacking sufficient information on the long-term outcome, and while ignoring the fact that these therapies may paradoxically have devastating long-term outcomes in some patients. Our data suggest that during the subacute stage of DiHS/DRESS, rapid immune recovery is the major driving force of the progression to autoimmune sequelae on the one hand and severe infectious complications, including cytomegalovirus (CMV) reactivation, on the other. This hypothesis is yet to be fully evaluated, however, and will require long-term follow-up of DiHS/DRESS patients.

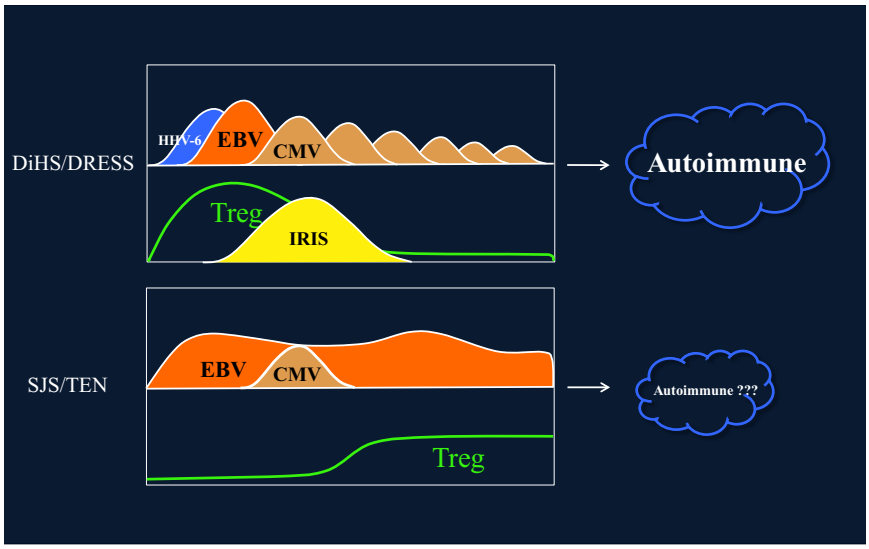

FIGURE 1 Disease course of DiHS/DRESS and SJS/TEN with their long-term sequelae

3 | PREDICTION OF DEVASTATING OUTCOMES

In DiHS/DRESS, frequent deterioration or several flare-ups of clinical symptoms often occur beyond the point in which the causative drug would be expected to have been eliminated from the body,[4,14] probably reflecting sequential reactivations of herpesviruses. Among herpesviruses sequentially reactivated, CMV reactivation occurring four to eight weeks after the onset of DiHS/DRESS can often lead to fatal outcomes. CMV reactivation occurring four to eight weeks after onset could be regarded as the most important factor for the prognosis, because our retrospective study clearly demonstrated that fatal outcomes are exclusively observed in patients with CMV reactivation.[18] Various clinical symptoms and complications traditionally considered to be unrelated to the drug eruptions or CMV reactivations may develop at various time-points after onset, making it difficult to predict the prognosis. We therefore investigated whether CMV reactivation could be involved in the development of severe complications occurring after clinical resolution and, if so, whether antiviral agents, particularly anti-CMV agents, could prevent the later development of severe complications, either CMV-related or CMV-unrelated. Our results clearly demonstrated that fatal outcomes and severe complications such as myocarditis and gastrointestinal bleeding were never observed in the CMV reactivation-negative group, suggesting that severe complications, traditionally regarded as either being related or unrelated to CMV reactivations, may develop in association with CMV reactivation. In support of this possibility, either CMV-related or CMV-unrelated complications developed 5 to 15 days after the detection of CMV reactivation, and the occurrence of these severe complications was mostly prevented in patients in whom anti-CMV therapy was initiated within three days after detecting CMV reactivation.[19] These results suggest that most, if not all, of the complications traditionally considered related or unrelated to CMV reactivations are due to CMV reactivation or related events and would therefore be preventable with anti-CMV therapy.

Because these complications would be treated by nondermatologists who did not care for the patients at the acute stage, the relationship between DiHS/DRESS, and the later development of such fatal complications has received little attention unless suspected from the patients' history. Our results also showed that age over 70 years is associated with the highest risk of later development of CMV reactivation, especially CMV-related fatal complications.[19] Because these complications and autoimmune sequelae occurred around two months (complications) and two to three years (autoimmune sequelae) after onset, respectively, the risk of such late-onset complications and autoimmune sequelae should be carefully considered even in low-risk patients under 60 years of age. Thus, simply measuring the therapeutic efficacy in the short term could be insufficient and follow-up examinations in DiHS/DRESS patients would be required for at least three years, even after complete resolution is observed. DiHS/DRESS is a serious disease with increased risk of viral reactivation, complications, autoimmune sequelae, and mortality. The resolution of DiHS/DRESS at the acute stage should no longer be loosely referred to as cured, because our data strongly support the need for improved long-term management for these patients, especially for these serious complications that occur after one to two year disease-free intervals.

4 | DERMATOSES OCCURRING AFTER OR DURING AN EPISODE OF HERPES ZOSTER

The usual clinical features of herpes zoster (HZ) are readily recognized. In most cases, the characteristic features of HZ rash establish the clinical diagnosis. Varicella zoster virus (VZV), however, also has an atypical presentation. These lesions encompass folliculitis,[20] syringitis, verruciform lesions,[21] nodular lesions,[22] intracranial hemorrhage,[23] and acute abdomen.[24] Involvement of the hair follicles or eccrine epithelium by VZV is an infrequently described histologic pattern mostly reported in HIV-infected patients and rarely reported even in immunocompetent patients. In these lesions, VZV DNA and

VZV-specific antigens such as VZV major envelope glycoprotein (gE) are detected in follicular keratinocytes, the epithelium of eccrine glands, or the gastric epithelium, which may be associated with cytopathic changes with intranuclear inclusions. The diagnosis of HZ can be also confirmed by polymerase chain reaction (PCR) analysis for VZV in the cerebrospinal fluid. Pruritus is also reported in many patients with HZ, not only during the herpetic period, but also in the pre- or postherpetic period. VZV gE can be detected as early as two to three days after the onset of HZ, and expression persists for at least several months in HZ lesions, whereas VZV DNA disappears much earlier than VZV gE antigens.[3] Because VZV gE is an essential late protein expressed on the cell membrane during lytic infection and is a predominant component of the virion envelope,[24,25] immunohistochemical detection of VZV gE in these lesions, either cutaneous or gastrointestinal, suggests VZV involvement in the development of these lesions.

Severe abdominal pain may occur as a serious manifestation of HZ, known as abdominal zoster,[26,27] particularly in an immunosuppressed host.[27] In these patients, the diagnosis of abdominal zoster is not usually considered until the typical vesicular eruptions begin to appear. Because the typical vesicular eruptions could be entirely absent in some patients with abdominal zoster,[28] however, the diagnosis in the setting of the absence of cutaneous lesions (zoster sine herpete) can only be made by PCR analysis of blood or saliva and biopsy or autopsy samples. Indeed, autopsy studies reveal high frequencies of abdominal involvement of VZV.[27] In these cases, herpetic lesions on the serosal and mucosal gut wall were observed at laparotomy. In this regard, our previous immunohistochemical study clearly demonstrated that detection of VZV antigens in the eccrine epithelium can be used as a highly reliable and useful clue to the diagnosis of HZ with unusual manifestations and inflammatory dermatoses induced by VZV infection.[3]

Immunoglobulin A vasculitis (IAV) may develop before or after the appearance of varicella or zoster rash,[28,29] and therefore, we hypothesized that IAV associated with gastrointestinal symptoms results from VZV reactivation. Consistent with this hypothesis, there are similarities in the nature of the abdominal pain and endoscopic findings in gastrointestinal lesions between patients with IAV and gastric or enteric zoster.[30] We therefore investigated whether VZV gE antigens could be detected in both cutaneous and gastrointestinal lesions, and whether a significant increase in VZV IgG titers could be specifically detected in IAV patients with severe abdominal pain.[31,32] We analyzed consecutive IAV patients with severe abdominal manifestations in a hospital-based adult population. The majority (84.6%, 16/19 cases) of severe abdominal pain-positive IAV patients also had arthralgia and developed a palpable purpura distributed over the extremities, most of them extending to areas above the waist. The most remarkable difference between abdominal pain-positive IAV and pain-negative IAV patients was the mean VZV IgG titers in the resolution stage; more than six months after onset, VZV IgG titers were drastically increased in only abdominal pain-positive patients and not in abdominal pain-negative patients ($209.2 + 57.6$ vs $14.5 + 2.5$, $P = 0.01$). Interestingly, most (76.9%) of the abdominal pain-positive patients were treated with systemic prednisolone at a dose of 0.5-1 mg/kg/d for one to two weeks, tapering down to 0.25-0.5 mg/kg/d over the subsequent two weeks. Nine IAV patients with abdominal pain underwent upper gastrointestinal endoscopy and biopsies were obtained during the endoscopy. Importantly, VZVgE antigens were identified in the foveolar epithelium adjacent to gastric ulcers as well as in the eccrine glands in seven of eight IAV patients with abdominal pain. These findings suggest that gastrointestinal lesions as well as cutaneous lesions in IAV could be induced by VZV reactivation and that abdominal pain associated with IAV could result from gastric zoster. Although patients with abdominal zoster reportedly have a high mortality rate despite initiation of the appropriate antiviral therapy,[26,27] the abdominal pain observed in VZV-related IAV resolved without antiviral therapy. It is likely that some abdominal symptoms observed in VZV-related IAV represent an extracutaneous manifestation of VZV reactivation, as in abdominal zoster, but the symptoms observed in the IAV patients would be less severe than those in abdominal zoster in immunocompromised hosts. The gastrointestinal manifestations of VZV-related IAV are likely to respond well to systemic prednisolone therapy alone. It may be important to balance the need to ameliorate the symptoms by prednisolone treatment with the desire to maintain the patient on effective anti-VZV therapy.

The term "postherpetic isotopic response" or "Wolf's isotopic response" encompasses a wide spectrum of clinical entities, ranging from LP to sarcoid granuloma.[33–35] Among them, granulomatous reactions ranging from granuloma annulare to granulomatous vasculitis at sites of resolved HZ lesions are well described.[34,36] These granulomatous reactions can occur immediately after the resolution of vesicular lesions, or at various times after the HZ. Earlier studies using PCR, however, failed to identify VZV DNA in the granulomatous reactions arising between one month and up to four years after the resolution of HZ.[37] These results may indicate that persistent expression of VZV gE antigens in the resolved HZ lesions could induce VZV-directed immune responses.

In addition to granulomatous reactions, many cutaneous disorders occur within healed HZ lesions, including LP, lichen simplex chronicus,[38] pseudolymphoma,[39] psoriasis,[40] lichenoid chronic graft-vs-host disease,[41] and lymphoma.[42] The term "postherpetic isotopic response" or "Wolf's isotopic response" describes the occurrence of a new, unrelated disease appearing at the same location as previously healed HZ or, rarely, herpes simplex lesions. At present, however, there are no satisfying explanations for how these cutaneous disorders develop at the healed herpetic lesions. Recent reports on herpetic syringitis suggest the involvement of sweat glands in VZV infection.[43] Although localized unilateral hypohidrosis with a dermatomal or segmental distribution is suggestive of VZV involvement, a relationship between localized hypohidrosis and VZV infection has not yet been demonstrated, probably due to the low frequency of detection of VZVDNA in the lesions. Nevertheless, in view of our recent observation that long-lasting hypohidrosis localizing to the involved dermatome in healed HZ lesions is relatively common,[44] hypohidrosis after HZ might contribute to the onset of these

secondary isotopic diseases at the involved dermatomes. We recently experienced two patients who developed LP and LA, respectively, in healed HZ lesions, prompting us to question whether hypohidrosis after VZV reactivation could be involved in the development of these isotopic responses. Because these lesions were characterized by dry skin and thought to be induced by postherpetic hypohidrosis, we examined sweating responses to thermal stimulation in these lesions using the impression mold technique, which allows for accurate quantification of the activity of each sweat gland/duct to produce and deliver sweat.[45] Sweating responses, as evidenced by the number of sweat droplets before and after thermal stimulation, were significantly decreased in the center of the LP and LA papules compared with those in an uninvolved area. Interestingly, dermicidin, a sweat-specific component, was immunohistochemically detected within the sweat glands/ducts as well as in the dermis adjacent to the sweat gland and epidermis in these isotopic lesions, suggesting that hypohidrosis could be induced by sweat leakage into the dermis and epidermis. Aimed at ameliorating hypohidrosis in these patients, treatment with a moisturizer, heparinoid, under occlusion was initiated based on its proven effectiveness in various lichenoid skin diseases characterized by sweating disturbances.[45] Three weeks after beginning the moisturizer therapy under occlusion, the papules had flattened completely in association with prompt and impressive relief of the pruritus. In view of recent findings that normal human sweat contains proteolytic enzymes, interleukin (IL) -1 α, IL-1 β, IL-6, IL-8, IL-31, and tumor necrosis factor (TNF) -α, most of which induce leukocyte recruitment to the skin,[46–49] skin-directed migration of T cells might be initiated and further amplified by sweat leakage. Thus, our findings could indicate that sweat leakage from fragile sweat glands/ducts due to VZV infection triggers the development of postherpetic isotopic responses. In addition to LP and LA, syringotropic granulomas could also develop upon sweat leakage around the sweat glands. Consistent with this view, we previously described a syringotropic variant of cutaneous sarcoidosis characterized by marked syringotropism of epithelioid histiocytes, exhibiting defective sweating responses to thermal stimulation[50]; such tropism of epithelioid cells to sweat glands, however, was only detected in the early stage of the lesions. Treatment of postherpetic isotopic responses is usually symptomatic and the application of topical corticosteroids is generally thought to be effective. Topical corticosteroids are often used with mixed results, however, and our findings suggest that continued treatment with topical corticosteroids that may deteriorate sweating function is not appropriate. Although it is unlikely that hypohidrosis is responsible for all postherpetic isotopic responses, some diseases, such as some LP and LA, result from hypohidrosis occurring after HZ. Thus, in the case of postherpetic isotopic responses characterized by sweating disturbances, topical moisturizer in conjunction with discontinuation of topical corticosteroids often produces dramatic improvement in otherwise refractory lesions. We coined the term "postherpetic hypohidrosis-related isotopic response" to refer to the association between the clinical features common to a distinctive group of patients with postherpetic hypohidrosis. Localized hypohidrosis as evidenced by decreased sweating responses to thermal stimulation is a relatively common sequel of HZ but most of these cases may go unrecognized due to the absence of apparent clinical symptoms. Unless a history of HZ is sought in patients characterized with isotopic responses in a dermatomal distribution, the lesions would remain idiopathic.

5 | EFFECTS OF CORTICOSTEROIDS ON IMMUNE RESPONSES

Although the actions of corticosteroids are generally thought to be immunosuppressive, in some cases their actions may be immunostimulatory. Evidence is accumulating that stress-induced enhancement of immune function could be mediated by the action of corticosteroids in the acute phase of a stress response. Thus, the effect of corticosteroids may differ depending on the status of the activation of immune cells and tissue microenvironment in which the immune cells are activated. In addition, there may be confusion between a direct drug effect and an unanticipated consequence of a decrease in the dose of corticosteroids. As described above, the development of IRIS can also occur in non-HIV patients receiving immunosuppressive agents, such as prednisolone and tumor necrosis factor -α inhibitors, upon their reduction and withdrawal.[51] Based on these considerations, we postulate that withdrawal of corticosteroids could potentiate immune responses against tumors when applied before antitumor therapy (Figure 2).

Despite the initial enthusiasm for topical imiquimod (IMQ) as a novel treatment modality for malignant neoplasms, a recent review article concluded that its efficacy is limited to a given disease setting.[51] Thus, an adjunct therapy that can improve the antitumor efficacy of IMQ is needed. We initially hypothesized that decreasing the recruitment of Treg cells at the tumor site prior to IMQ therapy would have therapeutic value, because our previous unpublished preliminary study on IMQ monotherapy showed that Treg cells occur in significantly lower frequencies in dermal infiltrates of Bowen's disease lesions before treatment in patients who eventually exhibited a complete response compared to patients with a partial response. Starting IMQ therapy at a time when the frequency of Treg cells is lowest could be essential for achieving more robust immune responses to tumor cells. We conducted an open-label, nonrandomized study to investigate whether sequential therapy with topical corticosteroids and IMQ could produce a higher clearance rate for Bowen's disease than IMQ monotherapy.[52] Patients with Bowen's disease were assigned to either IMQ monotherapy or sequential therapy. A complete response occurred at 8 weeks in all patients receiving the sequential therapy, but only in some patients in the IMQ-treated group (37.5%). Our immunohistochemical analysis showed that sequential therapy greatly improved the antitumor efficacy of IMQ by excluding tumor-associated Tregs from the lesions before starting IMQ therapy. We recommend using topical corticosteroids before IMQ therapy to provide marked pain relief and an excellent subsequent response to IMQ, because prior therapy with topical corticosteroids before starting IMQ therapy reduced adverse

reactions such as local skin irritation at the application site and none of the patients discontinued the therapy because of such adverse events. Particularly in the treatment of large or very sensitive areas such as the genitalia, topical corticosteroids may have a strong effect not only for enhancing the treatment efficacy of IMQ, but also for reducing pain. Our immunohistochemical studies clearly demonstrated that Treg cells were more profoundly deleted from tumor lesions after a two-week treatment with topical corticosteroids, whereas $CD8^+$T cells were recruited to the lesions more rapidly than Treg cells after starting IMQ therapy (Figure 3). Such time-dependent changes in the pattern of T-cell recruitment in sequential therapy were reflected by the dramatic increase in the ratio of $CD8^+$T cells to Treg cells at two to four weeks after starting IMQ therapy.[52] Thus, the use of topical corticosteroids, when induced before antitumor therapy, enhances the antitumor effects of IMQ on the one hand, but may aggravate the consequences of contact sensitization on the other hand. It is therefore necessary to examine whether frequent withdrawal of topical corticosteroids paradoxically aggravates atopic dermatitis lesions in patients with atopic dermatitis where the immune system has already been Th2-primed by allergens. If so, topical corticosteroids may have both antiinflammatory and immunopathologic effects, depending on the situation in which topical corticosteroids are used.

6 | CONCLUSION

Anticytokine therapies have recently received special attention as treatment modalities for allergic diseases. Detailed characterization of the timeline of the immunologic events occurring in patients treated with these anticytokine therapies, however, is necessary. Although IL-4/IL-13 blockade is considered most effective in ameliorating atopic inflammation, it remains unknown whether these anticytokine therapies could have beneficial long-term outcomes when used over a prolonged period of time. It is not clear whether long-term inhibition of the activity of these cytokines will be safe in

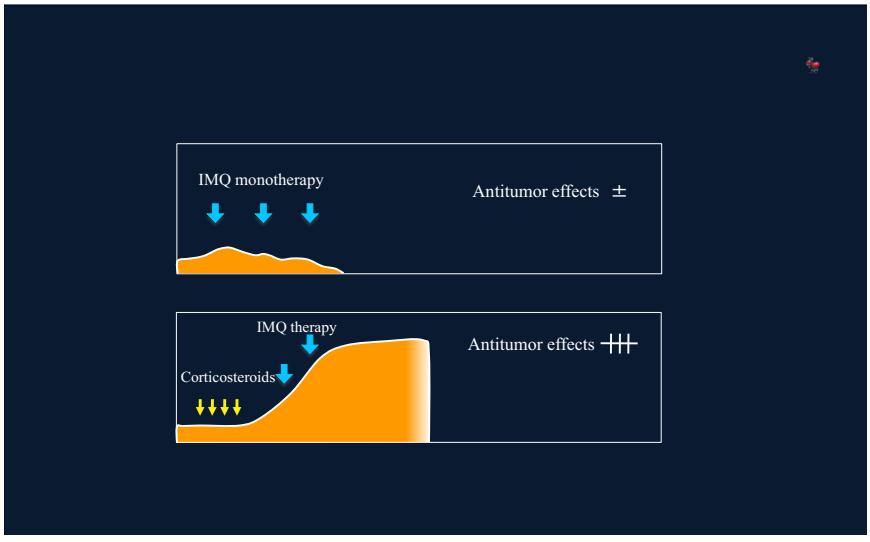

FIGURE 2 Difference in the antitumor efficacy between IMQ monotherapy and sequential therapy with topical corticosteroids and IMQ

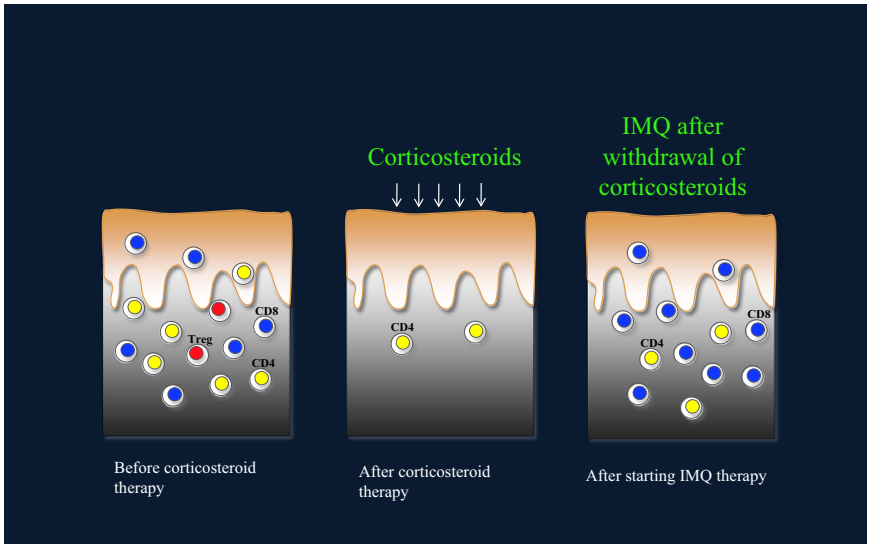

FIGURE 3 Histopathologic evolution of Bowen's disease lesions sequentially treated with topical corticosteroids and IMQ

humans. These previous analyses were largely performed in mouse models, and thus more patient-based studies are required to address these important issues given the differences in skin physiology between human and mice.

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