Title

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Journal

Journal of Drugs in Dermatology, 24(3)

ISSN

1545-9616

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Publication Date

2025-03-01

DOI

10.36849/jdd.7828

doi:10.36849/JDD.7828

 ORIGINAL ARTICLE

Alopecia as an Adverse Event of Immune Checkpoint Inhibitor Therapies: Clinical Evidence and Outcomes

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ABSTRACT

Immunotherapy utilizing immune checkpoint inhibitors (ICIs) such as PD-1, PD-L1, and CTLA-4 inhibitors has revolutionized cancer therapy by enhancing T cell recognition and attack against cancer cells.[1] Immune-related adverse events (irAEs) are a limitation of ICI therapy, encompassing various manifestations such as colitis and cutaneous adverse events such as dermatitis, alopecia, and vitiligo.[2] Hair loss is a common concern of cancer patients as they embark on their therapeutic paths. The evidence on alopecia from isolated clinical trials with ICI therapies is limited and largely lacks diagnostic and prognostic details to help guide patients.[3,4] In this systematic review, we examined the types of alopecia as part of the irAEs of ICI therapy, timing of onset, prognosis, and treatment approaches. Our analysis includes 19 studies describing new-onset non-scarring or scarring alopecia following ICI treatment. Alopecia was a rare adverse event in the setting of ICIs (n=26) with the onset of alopecia occurring within one year of initiating treatment. Slightly over half of the affected patients reported some degree of hair regrowth after attempted alopecia-directed treatments. We discuss available data to increase awareness of this rare but potentially permanent side effect of ICI therapy. Further research is warranted to enhance our understanding of alopecia as an irAE and to optimize patient management strategies.

J Drugs Dermatol. 2025;24(3):255-260. doi:10.36849/JDD.7828

INTRODUCTION

Immune checkpoints are inhibitory pathways within the immune system that maintain self-tolerance and regulate the duration and strength of immune responses.[1] Tumors can exploit this mechanism to evade immune surveillance by upregulating the expression of checkpoint molecules, downregulating major histocompatibility complex (MHC) molecules, producing immunosuppressive factors, and altering the tumor microenvironment.[1]

To combat this mechanism, immunotherapy with immune checkpoint inhibitors (ICIs) has emerged as a revolutionary therapy for cancers such as metastatic malignant melanoma, non-small cell lung cancer, and urethral carcinoma.[5] ICIs work by blocking the interaction between checkpoint proteins with their partner proteins, thereby suppressing the inhibitory signaling and allowing the T cells to recognize and attack cancer cells.[6]

Currently, the most widely used ICIs target the programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptors.[6] PD-1 inhibitors bind to the receptor on T cells to block the PD-1/PD-L1 immune-suppressing interaction.[7,8] Examples of these agents include pembrolizumab, nivolumab, and cemiplimab. PD-L1 inhibitors target the ligand portion of the PD-1/PD-L1 interaction and include agents such as atezolizumab, avelumab, and durvalumab.[7,8] CTLA-4 inhibitors such as ipilimumab indirectly regulate CD28/B7 interaction to promote T-cell activation.[9,10]

Despite their therapeutic impact, ICIs are not without limitations. Many studies have shown irAEs due to their modulation of the immune system. These irAEs include skin rash, hypothyroidism, and GI toxicity.[2,11,12] Recently, alopecia has been reported as a rare side effect in patients, however, details to guide patients while on therapy are lacking.[3] The evidence concerning the causal relationship between ICI therapy and alopecia is limited, necessitating further studies to better understand this potential adverse effect. Given the significant physiological stress alopecia can cause, early diagnosis and timely treatment are crucial.[13] Here, we aim to summarize the data on alopecia, both non-scarring and scarring, following ICI therapy, to gain insights into onset, prognosis, and potential treatments.

MATERIALS AND METHODS

A PubMed literature search following the PRISMA guidelines was conducted on April 2023 with the following keywords: "(immune checkpoint OR nivolumab OR pembrolizumab OR cemiplimab OR dostarlimab OR atezolizumab OR avelumab OR durvalumab OR ipilimumab OR PD-1 OR PD1 OR PD-L1 OR PDL1 OR CTLA4 OR CTLA-4) AND (alopecia OR hair loss)" and "(immune checkpoint OR nivolumab OR pembrolizumab OR cemiplimab OR dostarlimab OR atezolizumab OR avelumab OR durvalumab OR ipilimumab OR PD-1 OR PD1 OR PD-L1 OR PDL1 OR CTLA4 OR CTLA-4) AND (scarring OR cicatricial OR lichen OR frontal OR lupus OR chronic cutaneous lupus OR graham-little OR mucinosa OR central centrifugal OR folliculitis OR dermatosis)". Inclusion criteria included clinical trials, case reports, case series, and retrospective studies that discuss the onset of both non-scarring and scarring alopecia as a side effect of immunotherapy. Exclusion criteria included articles that discuss mixed use of immunotherapy (Figure 1). Data from relevant studies included study type, patient demographics, diagnosis, type of ICI, number and intervals of ICI treatments, onset of alopecia after first/initial ICI treatment, alopecia diagnosis, treatment of alopecia, and hair regrowth outcome.

RESULTS

A total of 19 articles were identified after screening: 17 case reports, 1 randomized controlled trial, and 1 retrospective case study (Figure 1, Table 1). Twenty-seven patients who experienced hair loss following ICI therapy were identified among these records. Among 26 patients, 14 received treatment with PD-1 inhibitors, 2 with PD-L1 inhibitors, and 3 with CTLA-4 inhibitors. Seven patients received a PD-1 and CTLA-4 inhibitor combination therapy. Alopecia onset occurred 2 to 9 months after the initiation of immune checkpoint inhibitor (ICI) therapy. Of 20 patients who received treatment for hair loss, 12 (60%) reported hair regrowth.

PD-1 Inhibitor (Nivolumab, Pembrolizumab)

PD-1 inhibitors were the most commonly listed ICI in patients who experienced hair loss. It is unclear if this is due to PD-1 inhibitors being most commonly prescribed. Fourteen patients in this study have solely used PD-1 inhibitors (nivolumab n=7, pembrolizumab n=7).[14-25] Alopecia areata (AA), lichen planoplanus (LPP), eosinophilic folliculitis, and erosive pustular dermatosis of the scalp (EPDS) were noted as an irAE. Patients were being treated for malignancies such as melanoma,

FIGURE 1. PRISMA Diagram. Process of inclusion of studies.

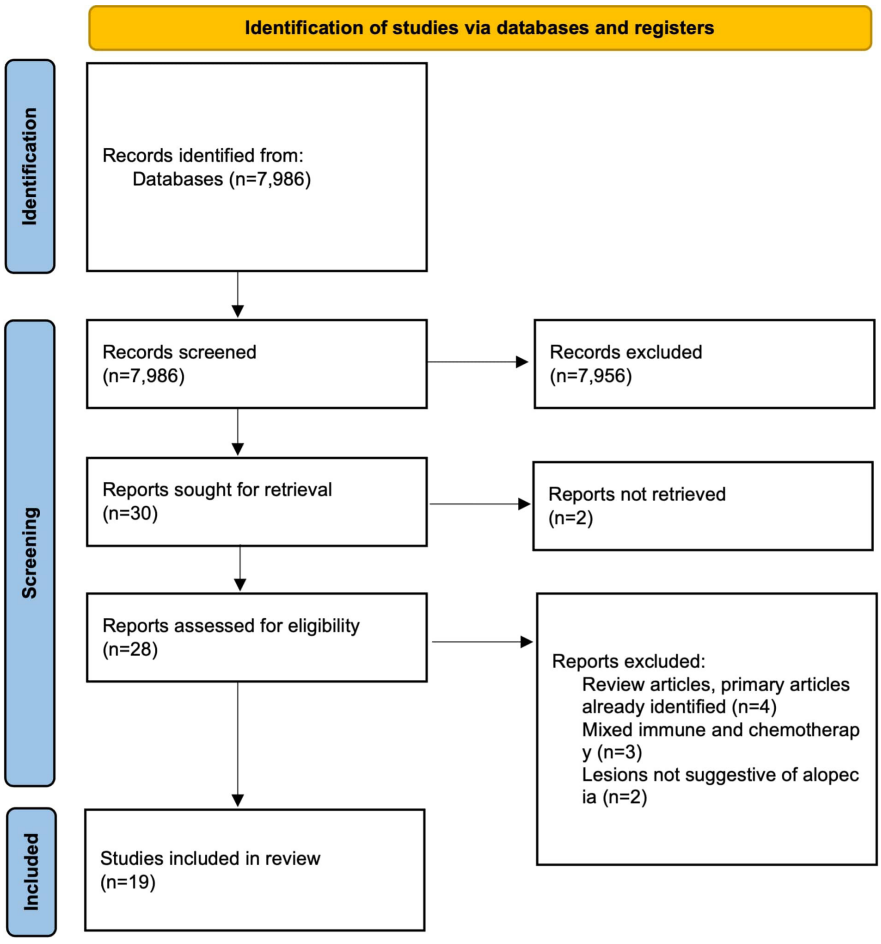

TABLE 1.

Summary of Current Literature on Alopecia as a Side-Effect of Immune Checkpoint Inhibitor Therapy

Authors (Year)	Study Type	Patient Age, Gender	ICI Type	ICI treatment duration	Alopecia Onset (time after first treatment, unless specified)	Alopecia Diagnosis	Treatment for Hair Loss	Regrowth after Treatment?
PD-1 Inhibitors								
Guidry et al (2018)	CR	64, F	Pembrolizumab	Unknown	9 months	AA	Treatment declined	Y
Kim et al (2021)	CR	55, M	Nivolumab	6 months	5 months	AA	Triamcinolone intralesional injections, topical steroids, minoxidil	N
Uthayakumar et al (2021)	CR	62, F	Pembrolizumab	2 years	9 months	LPP	Clobetasol lotion, 0.1% topical tacrolimus, oral doxycycline started, hydroxychloroquine 200 mg, prednisolone, triamcinolone scalp injection, 5% minoxidil topical, 0.1% tacrolimus topical	N
Rossi et al (2020)	CR	65, M	Nivolumab	Unknown	2 months	Eosinophilic folliculitis	Clobetasol propionate cream, topical lotion (2.4% minoxidil, 0.08% hydrocortisone butyrate)	N
Braasch et al (2022)	CR	76, F	Pembrolizumab	2.5 years	2 years	LPP	Topical clobetasol 0.5 mg/g solution	Unknown
	CR	63, F	Nivolumab	Unknown	16 weeks	LPP	Topical clobetasol 0.5mg/g	Unknown
Elshimy et al (2019)	CR	59, M	Pembrolizumab	Unknown	21 months	AA	Unknown	Unknown
Galli et al (2019)	CR	58, M	Nivolumab	Unknown	23 months	AA (universalis)	Topical steroids	N
Lakhmiri et al (2018)	CR	54, F	Nivolumab	26 months	6 months	AA (universalis)	Clobetasol gel and foam, intralesional triamcinolone	N
	CR	64, F	Nivolumab	30 months	15 months	AA	Foam and shampoo corticosteroid	Y
Magile et al (2020)	CR	72, M	Nivolumab	Unknown	2 months	EPDS	None	Y
Garcia-Melendo et al (2022)	CR	62, M	Pembrolizumab	Unknown	16 weeks	LPP	Clobetasol propionate 0.05% lotion once daily	Y
Hara et al (2022)	CR	73, M	Pembrolizumab	Unknown	6 months	AA	Topical steroids and phototherapy for 2 months	Y
Shen et al (2018)	RCS	67, M	Pembrolizumab	Unknown	18 weeks	AA	Unknown	Unknown
PD-L1 Inhibitors								
Kinoshita-Ise et al (2019)	CR	79, F	Atezolizumab	Unknown	4 weeks	AA	clobetasol lotion, minoxidil 5% foam on scalp	Y
Domingues-Santas et al (2021)	CR	61, M	Avelumab	Unknown	6 months	LPP	Clobetasol propionate 0.05% solution QD. 2 weeks, then twice a week for maintenance Doxycycline 100 mg QD for 3 months	Y
CTLA-4 Inhibitors								
Assi et al (2013)	CR	54, M	Ipilimumab	1-2 months for induction, 34 months for maintenance	1-2 months	AA (universalis)	Unknown	Unknown
Pearson et al (2019)	CR	88, M	Ipilimumab	12 weeks	17 months after last treatment	AA	Unknown	Unknown
Jaber et al (2006)	RCT	35, M	CTLA-4 inhibitor	Unknown	7 weeks	AA (universalis)	Bland emollients (no topical steroids)	N
Combined ICI Therapy								
Zarbo et al (2017)	CR	67, F	CTLA-4 and PD-1 inhibitors (Unspecified)	Unknown	6 months after last treatment	AA	Clobetasol foam, biotin, and orthosilicic acid	Y
		65, F	CTLA-4 and PD-1 inhibitors (Unspecified)	Unknown	3 months after last treatment	AA	Unknown	Y
		62, M	CTLA-4 and PD-1 inhibitors (Unspecified)	Unknown	After 3 cycles	AA (universalis)	Unknown	N
Cogen et al (2018)	CR	47, M	Pembrolizumab + Ipilimumab	Unknown	2 months	LPP	Prednisone, systemic minocycline and topical clobetasol	Y
Lakhmiri et al (2018)	CR	29, F	Ipilimumab + Nivolumab (2 months), Maintenance Nivolumab (15 months)	2 months; maintenance 15 months	4 months	AA	Topical corticosteroid cream and sham-poo, intralesional injections of triamcinolone	Y
	CR	33, F	Ipilimumab + Nivolumab / 4 infu-sions / 3 weeks	8 months	After 3 cycles	AA	Topical corticosteroid cream	Y
Braasch et al (2022)	CR	62, F	Nivolumab + Ipili-mumab, Nivolumab monotherapy after	1.5 years	2.5 months	FFA	Topical clobetasol 0.5 mg/g solution	N

CR = Case Report, RCT = Randomized Controlled Trial, AA = Alopecia areata, LPP = Lichen Planopilaris, EPDS = Erosive pustular dermatosis of the scalp, FFA = Frontal fibrosing alopecia

hepatocellular carcinoma, and renal cell carcinoma. Median age was 63.5 and 6 women were identified among the 14 patients. The median onset of alopecia after treatment initiation was 30 weeks (7.5 months). Prognosis of alopecia varied, where 5 patients experienced reversal of hair loss and other 5 patients experienced no regrowth or worsening of alopecia. 2 patients of the 10 discontinued ICI therapy after hair loss. Outcomes of 4 patients were not reported.

Clinical presentation of alopecia varied widely among patients. A 64-year-old female was diagnosed with AA 9 months after starting treatment with pembrolizumab for superficial spreading melanoma.[14] Despite not receiving any alopecia-directed treatment, the patient experienced achieved complete hair regrowth after 5 months while continuing ICI therapy. In contrast, a 55-year-old male diagnosed with AA 5 months after starting treatment with nivolumab for hepatocellular carcinoma progressed to alopecia totalis despite treatment with topical steroids and topical minoxidil.[15]

The use of ICIs has been associated with the development of cicatricial alopecia in 6 patients.[16-18,22,23,27] Scarring alopecias are driven by an inflammatory process that can cause irreversible damage to hair follicles.[26] LPP was diagnosed in 4 patients; one with eosinophilic folliculitis, and another with EPDS. Patient ages ranged from 62 to 76 with an equal gender distribution. The median onset of alopecia was 16 weeks after therapy initiation.

A 62-year-old female diagnosed with LPP 9 months after starting pembrolizumab therapy for stage IV metastatic melanoma.[16] Despite treatment with clobetasol lotion, 0.1% topical tacrolimus, oral doxycycline, and a multitude of other treatments, there was no improvement in hair regrowth while staying on ICI treatment.

In addition, a 65-year-old male was diagnosed with eosinophilic folliculitis 5 months after starting treatment with nivolumab for metastatic clear cell renal carcinoma, but there was no improvement despite alopecia treatment.[17]

A unique case of EPDS was reported in a 72-year-old male after nivolumab treatment for metastatic squamous non-small cell lung cancer.[27] 2 months after treatment initiation, confluent hyperkeratotic plaques in frontal and parietal area were noted. Due to tumor progression, the patient discontinued ICI therapy, which markedly improved scalp lesions without any alopecia-directed treatment.

PD-L1 Inhibitors (Atezolizumab, Avelumab)

Two cases of alopecia, non-scarring AA and scarring LPP, have been reported as irAEs of PD-L1 therapy.[28,29] Both patients responded positively to alopecia-specific treatment and reported hair growth with decreased pruritus.

AA as a side effect of PD-L1 inhibitors was reported in a 79-year-old female.[28] After 4 weeks of starting atezolizumab for ureteral cancer, ICI therapy was halted immediately, but no growth of hair was noted. The patient demonstrated significant hair regrowth after treatment with clobetasol lotion and topical minoxidil.

LPP was described in a 61-year-old male 24 weeks after starting avelumab.[29] The patient had a prior history of androgenic alopecia (AGA) but developed diffusely erythematous scalp with perifollicular hyperkeratosis after starting PD-L1 treatment. Hair regrowth was achieved with clobetasol propionate 0.05% solution with maintenance doxycycline 100 mg for 2 months even with continuation of ICI therapy.

CTLA-4 Inhibitors (Ipilimumab)

Two case reports and one randomized control trial identified three patients who developed alopecia areata between 4 weeks and 1.5 years after starting treatment.[30-32] One patient reported no growth of hair after minimal treatment, while the remaining two patients have no mention of alopecia prognosis.

An 88-year-old male with metastatic melanoma experienced patchy scalp hair loss after ipilimumab treatment over 12 weeks, but was not diagnosed with AA until 1.5 years after completing his treatment.[31] While a weak and delayed link between ipilimumab therapy and AA can be presumed, the treatment and prognosis of the hair loss were not discussed.

A randomized controlled trial of 63 patients reported a 35-year-old male who experienced hair loss 49 days after starting a CTLA-4 inhibitor.[32] The patient was treated with bland emollients and oral diphenhydramine hydrochloride, but no hair growth was observed two months after completing the ICI treatment.

Combined Treatments

Seven patients were reported to develop varying forms of alopecia such as AA, LPP, and frontal fibrosing alopecia (FFA) after treatment with a combination of a PD-1 inhibitor and a CTLA-4 inhibitor in four case reports.[4,18,21,33] Of the 7 patients, 5 patients (71%) reported hair regrowth. 4 of these 5 patients were treated with a mix of topical clobetasol, systemic minocycline, or systemic prednisone. There was no mention of treatment regimen for the other patient with hair regrowth. The remaining 2 patients (29%) did not show hair regrowth, either with or without treatment. The general time of onset for alopecia ranged from 2 months after initiating treatment to 6 months after completing treatment.

DISCUSSION

Our in-depth search of the current literature on ICIs reports both non-scarring and scarring alopecia as potential side effects, found with low incidence of 1 to 2% of patients treated with ICI

as reported in a previous randomized clinical trial.[32] It is difficult to extrapolate and speculate from the available data on the prognosis of hair loss. Alopecia areata was the most common type of alopecia diagnosed among patients in this review (n=18). The onset of alopecia appears to typically occur between 2 to 9 months after starting treatment, with rare cases reported with onset greater than 12 months.

The mechanism behind immune checkpoint inhibitor therapy leading to alopecia areata alludes to the immune milieu created by ICI therapy, where T-cells activate against common antigens in normal tissues.[34] This general mechanism, when applied to hair follicles specifically, indicates that ICIs can disrupt the hair follicle immune privilege (HF-IP).[35] PD-1 pathway dysregulation has been suggested to contribute to hair follicles autoantigens, such as melanogenesis-associated proteins.[35,36] In addition, PD-L1 is significantly upregulated in the dermal papilla and dermal sheath cup cells in hair follicles.[37] Combined with the disruption of the cytotoxic T cell balance and HF-IP, ICI can allow cytotoxic T cells to react with the hair follicle autoantigens, causing T-cell mediated destruction implicated in scarring alopecias such as LPP.[38] Undiagnosed primary immunodeficiency syndromes such as CTLA-4 haploinsufficiency can also be a cause of these immune reactions.[39] Although rare, patients on ICI therapy should be thoroughly checked for immunodeficiency syndromes with further worsening of AA and unrelated comorbidities.

Treatment of ICI-induced alopecia should focus on addressing the immune disruption caused by ICIs to facilitate hair protection and regrowth. Data indicate that in both non-scarring and scarring alopecia, topical corticosteroids (n=17) were most commonly used treatment with topical clobetasol (n=11). Triamcinolone intralesional injections (n=4) were also used either alone or as an adjunct therapy. Other therapies included topical minoxidil (n=4) or oral antibiotics such as doxycycline or minocycline (n=3). These treatments are in line with the current mainstay treatment of both non-scarring and scarring alopecia.[3,40,41]

There are limitations to evaluating the occurrence of non-scarring or scarring alopecia after ICI usage in the published isolated reports and clinical studies. The absence of standardization in medication dose and intervals poses a challenge in evaluating any trends. Furthermore, there is potential for misdiagnosis due to the lack of dermatological assessment of alopecia. For instance, scarring alopecia leads to irreversible damage to the hair follicles, which may result in permanent hair loss. Albeit, some of the articles report near-complete hair regrowth in patients diagnosed with subtypes of scarring alopecia, raising concerns about the accuracy of the diagnosis and highlighting the need for more precise diagnostic approaches.[33]

To date, there are increasing reports of individuals presenting with different types of alopecia after ICI treatments. It is noteworthy that all the patients in the review presented only when there were overt symptoms (eg, severe pruritus, erythema). This raises the question of whether milder cases with slight erythema and inflammation are being underdiagnosed. Thus, surveillance of initial signs of scalp erythema and inflammation can allow early management of alopecia to reduce the number of patients who develop worsening alopecia. The impact of discontinuing ICI therapy on hair regrowth is unclear. Among 3 patients who discontinued ICI therapy while on alopecia-direct treatment, only 1 patient experienced regrowth. In contrast, 11 out of 17 patients who continued ICI therapy reported hair regrowth with alopecia-directed treatment. These findings suggest discontinuation may not affect hair regrowth, but a further study with larger sample is needed. Alopecia treatment should be started before considering the discontinuation of ICI therapy.

CONCLUSION

Both non-scarring and scarring alopecia following ICI treatment have primarily been discussed in case reports. The onset of alopecia typically occurs between 2 to 9 months after starting ICI therapy, but there have been reports of immediate onset and onset occurring 1.5 years after therapy completion. Hair regrowth was observed approximately 2 to 6 months after alopecia treatment in patients who responded well. The lack of standardized assessment among patients can impact the quality of the review. Although alopecia is not the most common irAE of ICIs, it warrants routine surveillance and monitoring to identify signs of scalp inflammation and erythema for early intervention and management.

DISCLOSURES

The authors have no conflicts or funding sources to disclose.

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