Skin Autoimmunity Secondary to Alemtuzumab in a Tertiary Care Spanish Hospital

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Abstract

Background and Objectives
The most common adverse events (AEs) after alemtuzumab (ALZ) include adverse infusion reactions, infections, and autoimmune disorders. Skin AEs are common during infusion, but there are few reported cases of long-term skin autoimmune disease.

Methods
A retrospective case series of patients developing long-term autoimmune skin disorders after ALZ administration in a tertiary care hospital.

Results
Of 133 patients treated with ALZ, 8 patients (6.02%) developed 9 autoimmune cutaneous AEs, including 4 events of alopecia areata, 2 of vitiligo, 2 of chronic urticaria, and 1 of inflammatory atrichia. Three of them occurred between the first and the second infusion.

Discussion
The lesions described are secondary to autoimmune disorders, probably related to immune dysregulation because of a differential lymphocyte repopulation after ALZ. Autoimmune cutaneous AEs may be frequent, and it would be recommended to monitor its appearance to treat them.
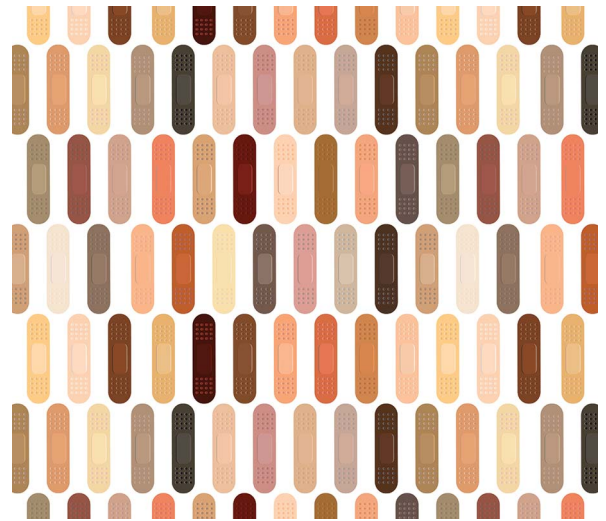
Alemtuzumab (ALZ) is an anti-CD52 monoclonal antibody approved for the treatment of relapsing-remitting multiple sclerosis.[1] ALZ binds to CD52, causing cell lysis and depletion of T and B lymphocytes, followed by a differential lymphocyte repopulation.[2] CD19 B-lymphocytes are repopulated during the first 3 to 6 months, reaching levels above normal at 12 months. CD8 T-lymphocytes take approximately 9–12 months to reach normal levels, whereas CD4 can take up to 1 or 2 years to reach normal levels.[3,4]

ALZ efficacy and safety has been evaluated in 3 pivotal studies: 1 phase II (CAMMS223) and 2 phase III (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis 1 [CARE-MS] and 2 [CARE MS-II]). All of them were randomized and compared with an active comparator (interferon β-1a).[5-7] The most commonly detected adverse events (AEs) detected with ALZ in such pivotal studies were adverse infusion reactions, increased risk of infections, and autoimmune disorders. The most common autoimmune disorders include thyroid events, autoimmune thrombocytopenia or other cytopenias (such as neutropenia or pancytopenia), and autoimmune nephropathies.[5-11]

Table Patient Characteristics

Case	Sex	Age[a]	Time (y) since diagnosis RRMS[a]	Previous DMT[b]	Skin disorder	Time of appearance	Other
1	Male	37	27	Glatiramer, fingolimod, and natalizumab	Alopecia areata	After second inf	Hypothyroidism
2	Female	27	7	Fingolimod	Vitiligo	Between first and second inf	—
3	Female	42	24	Interferon-B1b, natalizumab, glatiramer, fingolimod cyclophosphamide, and dimethyl fumarate	Vitiligo	Between first and second inf	—
4	Female	26	8	Clinical trial (siponimod) and dimethyl fumarate	Chronic urticaria	After second inf	Hyperthyroidism
5	Female	40	16	Fingolimod	Alopecia areata	After second inf	Seborrheic dermatitis
6	Female	40	18	Interferon-B1b, fingolimod, and natalizumab	Alopecia areata	After second inf	Atopic dermatitis
7	Female	36	10	Interferon-B1b, natalizumab, and fingolimod	Inflammatory atrichia and chronic urticaria	Between first and second inf After second inf	Allergic rhinitis
8	Female	31	6	Fingolimod and dimethyl Fumarate	Alopecia totalis	After second inf	—

Abbreviations: ALZ = alemtuzumab; DMT = disease-modifying therapy; RRMS = relapsing-remitting multiple sclerosis.
[a] Age and time since diagnosis when beginning ALZ.
[b] Last DMT before ALZ is remarked.

These autoimmune disorders peak between 2 and 3 years after the administration of ALZ but may occur beyond 5 years after its infusion.[3] The cause of secondary autoimmunity is still unknown, but different mechanisms have been proposed. One potential mechanism is differential lymphocyte repopulation, which can cause an imbalance in favor of B lymphocytes, favoring the production of autoantibodies in the absence of regulatory T cells.[3,4] Another proposed mechanism involves T cell repopulation pathway, with homeostatic proliferation of cells escaping depletion predominating over thymic reconstitution—resulting in a less varied repertoire of T lymphocytes driven by IL-21—that has been linked to a higher risk of secondary autoimmunity.[12,13]

Other autoimmune disorders after ALZ, such as myositis,[14] vasculitis,[15] hemolytic anemia,[16,17] or autoimmune hepatitis,[18] are reported in the clinical literature. Skin AEs are common during infusion of the drug, and pruritic skin rash is very frequent.[5-7] However, there are few published cases of long-term skin autoimmune diseases after ALZ. Recently, isolated cases of alopecia areata,[19,20] vitiligo,[21,22] and refractory chronic spontaneous urticaria[23] have been reported.

The aim of this study is to define the incidence and evolution of autoimmune skin AEs in a sample of patients after receiving ALZ.

Methods

We present a single-center, retrospective case series of patients developing autoimmune skin disorders after ALZ administration in a MS care unit of a tertiary care hospital (MS care Unit, Virgen Macarena Hospital, Seville, Spain).

Patients have received ALZ between April 2009 and June 2020, and the follow-up has been performed in our MS unit. Data collection was conducted in 2020.

The diagnosis, treatment, and follow-up of the described autoimmune skin diseases have been performed by dermatology physicians.

We recorded gender, age of patients at the time of ALZ treatment, time since MS diagnosis, time since ALZ administration, the number of ALZ courses received, previous disease-modifying treatment, the type of autoimmune skin condition, and other concomitant autoimmune diseases.

Categorical variables are presented as frequencies and percentages.

Standard Protocol Approvals, Registrations, and Patient Consents

Received written informed consent was obtained from all patients (or guardians of patients) participating in the study (consent for research).

Data Availability

Anonymized data will be shared by request from any qualified investigator.

Results

Of 133 patients treated with ALZ, 8 patients (1 man and 7 women) developed long-term autoimmune cutaneous AEs (8.27%), with an average age of 34.88 and an average time since diagnosis of 14.75 years. One patient developed 2 different lesions, with an overall of 9 reported skin lesions. Three of them occurred between the first and second infusion; the other 6 occurred after the second course of treatment. No skin disorders were detected in consecutive cycles. Three patients (37.5%) switched from fingolimod as previous disease-modifying therapy (DMT) before ALZ, 3 (37.5%) from dimethyl fumarate, and 2 (25%) from natalizumab. Table shows a summary of the characteristics of these patients.

Case 1

A man who received ALZ at the age 37 and after 27 years since diagnosis. Natalizumab was the previous DMT, stopped because of JC virus seroconversion. Thirteen months after the second infusion, he presented with hair loss on the bard and scalp and was diagnosed with alopecia areata (Figure 1). He started topical treatment with minoxidil, retinoic acid, and clobetasol and experienced clinical improvement. He also presented autoimmune hypothyroidism.

He is currently stable and does not need additional ALZ cycles.

Case 2

A woman who received ALZ at the age 27 and after 7 years since diagnosis after failure to fingolimod. Six months after the first infusion, she presented with hypopigmented macules on the limbs and genital area, appearing after a minor trauma. She was referred to dermatology and diagnosed with vitiligo with the Koebner phenomenon (Figure 2). Then, she began topical treatment with tacrolimus. After that, she received the second infusion. She is currently stable and does not need additional ALZ cycles.

Case 3

A woman who received ALZ at the age 42 and after 24 years since diagnosis after failure to dimethyl fumarate. She had failed several treatments before. Fifteen months after the first infusion, but before receiving the second cycle (it was delayed because of lymphopenia), she presented with hypopigmented macules and was diagnosed with vitiligo (Figure 3). Lesions remitted spontaneously without any treatment in a few months and did not show again after the second cycle. She needed no additional cycles.

Case 4

A woman who received ALZ at the age 26 and after 8 years since diagnosis after failure to dimethyl fumarate. Fourteen months after the second cycle, she presented with daily exanthematous and itchy lesions of less than 24 hours duration. She was referred to dermatology that described them as hives, and she was diagnosed with chronic spontaneous urticaria (Figure 4). Cyclosporine was proposed as the treatment from dermatology but was considered not convenient because of immunosuppression. She received several cycles of steroids, and nowadays, she maintains symptomatic treatment with antihistamines. She also presented Graves disease and Graves ophthalmopathy. She needed no additional cycles of ALZ.

Case 5

A woman who received ALZ at the age 40 and after 16 years since diagnosis after failure to fingolimod. Three months after the second cycle, she presented with hair loss located in her scalp and was diagnosed with alopecia areata (Figure 5). She is currently treated with topic methylprednisolone. After first infusion, she was diagnosed with seborrhoeic dermatitis too because of scalp peeling. She needed no additional cycles.

Case 6

A woman who received ALZ at the age of 40 and after 18 years since diagnosis. She had ceased natalizumab because of JC virus seroconversion. Twenty months after the second cycle, she presented with hair loss located in her scalp and was diagnosed with alopecia areata. She was treated with topic clobetasol and tacrolimus, and her evolution was favorable. She was then diagnosed with atopic dermatitis by dermatology because of peeling lesions on her back and arms. She needed no additional cycles.

Case 7

A woman who received ALZ at the age 36 and after 10 years since diagnosis after failure to fingolimod. A few months after the first infusion, she began to present with hair loss that was treated with biotin. Hair loss on the scalp improved, but she kept losing eyelash hair, with her condition worsening and presenting upper eyelid margin inflammation and pain after the second ALZ cycle. She was then referred to dermatology and diagnosed with inflammatory atrichia. In addition, 11 months after the second infusion, she began to present hives on her face of less than 24 hours duration and was diagnosed with chronic spontaneous urticaria that needed no treatment. She also presented allergic rhinitis as AE. She needed no additional cycles.

Case 8

A woman who received ALZ at the age 31 and after 6 years since diagnosis after failure to dimethyl fumarate. Nine months after second infusion, she began to present with patchy hair loss in several areas, suggesting alopecia areata (Figure 6). Lesions converged until total hair loss on the scalp. She was referred to dermatology and was diagnosed with alopecia totalis. After treatment with corticosteroids infiltrated into the scalp, followed by oral and topical corticosteroids and minoxidil, the hair is starting to grow again. She needed no additional cycles.

Discussion

In our series, we have evidenced different long-term skin AEs after ALZ treatment. These cases share an autoimmune origin with cutaneous manifestations. As mentioned, cases of vitiligo[21,22] and alopecia[19,20] have been described before; a case of chronic spontaneous urticaria has been recently described,[23] and dermatitis is also mentioned as an ALZ-related event.[24]

Figure 4 Hives in a Patient With Chronic Urticaria

Figure 5 Alopecia Areata

The pathophysiology of vitiligo has been widely described as an autoimmune phenomenon against skin melanocytes, leading to the appearance of depigmented areas. Alopecia areata is also determined by an autoimmune aggression around the hair follicle causing the growth to stop and its subsequent fall. We use the term alopecia totalis if it affects the whole scalp and alopecia universalis if it affects the body hair. CD8 T-lymphocytes are critically involved in these pathologies.[21,25]

Chronic spontaneous urticaria is determined by the appearance of wheals and/or angioedema for longer than 6 weeks. There are several theories of pathogenesis: the autoimmune origin is the most accepted hypothesis to explain inappropriate activation and degranulation of mast cells. Both a decrease in CD4 T-cells and an autoantibody-mediated disease process have been linked with this process and may explain its appearance after ALZ.[23,26]

ALZ is known to be associated with exanthems or dermatitis in the setting of therapy. These findings could be related to hypersensitivity reactions, but also to immune dysregulation.[24] That could explain the long-term incidence of newly diagnosed dermatitis shown in our patients because 2 of our reported patients also presented with dermatitis. In addition, 1 patient treated with ALZ that has not been included in this work presented itchy lesions that were described as an unspecified dermatitis, but lesions vanished before a formal

diagnosis could be established. We have not counted these lesions for the overall incidence because they have been heterogeneous, and the etiology is not clear because biopsies have not been performed.

Acne has been classically considered an infectious disease. However, it is an inflammatory process in which both innate immunity and propionibacterium acnes play an important role. It is related to other drugs that cause imbalance of innate immunity such as antiepidermal growth factor drugs.[27] We have detected an increased incidence of acne within our patients treated with ALZ (3 patients without previous history of acne). This leads us to consider a possible immune dysregulation role. However, we have decided not to count the acne lesions in the overall of this work because we cannot rule out an infectious cause.

According to our data, alopecia areata and chronic urticaria tended to appear after the second infusion. As mentioned, 1 patient presented with lesions 15 months after the first infusion but before receiving the second cycle. Thus, lesions detected after the second cycle may be a late consequence of the first infusion. In addition, we found no new appearance of skin lesions after additional cycles following the second one.

As mentioned, isolated adverse effects have been previously reported, but this is the first series of cases encompassing all skin adverse effects. Thus, it allows us, for the first time, to infer the incidence of these effects.

Figure 6 Alopecia Areata Evolving to Alopecia Totalis

The large cohort of patients treated with ALZ in our center allowed the detection of a wide variant of lesions in this study. Reported cases are supported by dermatology evaluations and photographic records.

Skin biopsies have not been performed, which, in some cases, prevents us from fully confirming the etiology of the lesions. In addition, cases are still too few to make assessments regarding the time of onset or incidence.

According to the overall prevalence (6.77%), autoimmune cutaneous AEs may be more frequent than other known autoimmune AE. Some of these findings may remain unnoticed if we are not vigilant to its appearance, so we recommend monitoring the appearance of cutaneous lesions that may be potentially treatable. Further studies to perform an accurate approach to the real prevalence of these injuries and its relation with autoimmunity and the drug are recommended.

Study Funding

Disclosure

Publication History

Appendix Authors

Name	Location	Contribution
Rocío López Ruiz, MD	Unidad de Esclerosis Múltiple, Hospital Universitario Virgen Macarena, Sevilla, España	Drafting/revision of the manuscript for content, including medical writing for content, major role in the acquisition of data, study concept or design, and analysis or interpretation of data
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Appendix *(continued)*

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