Daclizumab-induced adverse events in multiple organ systems in multiple sclerosis

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ABSTRACT

Objective: To report 3 patients with multiple sclerosis (MS) who presented with daclizumab-related adverse events (AEs) in multiple organ systems.

Methods: A retrospective chart review was performed of patients with MS who had clinical and histopathologic findings suggestive of daclizumab-induced AEs between 2004 and 2010 at the Johns Hopkins MS Clinic. This study met criteria for exemption from review from the institutional review board.

Results: Of 20 total patients with MS who had been treated with daclizumab, 3 patients with clinical and histopathologic findings suggestive of daclizumab-induced AEs were identified. All patients were treated with Zenapax (1 mg/kg monthly IV infusions) outside of a clinical trial setting. Clinical manifestations after a mean treatment duration of 20 months consisted of diffuse rash and alopecia, diffuse lymphadenopathy, and breast nodules. Tissue histopathology demonstrated lymphocytic infiltrates with CD56-expressing cells in 2 patients (lymph node, breast nodule). On daclizumab discontinuation, the rash/alopecia and diffuse lymphadenopathy resolved, while the breast nodules stabilized.

Conclusions: Daclizumab-induced AEs can occur in various organ systems after a relatively prolonged duration of exposure and require clinician awareness. Future studies are needed to better understand the relationship between natural killer cells and daclizumab-related AEs. *Neurology*® 2014;82:984-988

GLOSSARY

AE = adverse event; **FDG** = fluorodeoxyglucose; **IL-2** = interleukin-2; **MS** = multiple sclerosis; **NK** = natural killer.

Daclizumab is a monoclonal antibody targeted against CD25-expressing T cells that is emerging as a potentially useful therapeutic agent in multiple sclerosis (MS). Daclizumab's blockade of the high-affinity α -subunit (CD25) of interleukin-2 (IL-2) receptors limits IL-2 consumption by T cells but paradoxically allows cells that express more β - and γ -chains (natural killer [NK] cells and precursors of innate lymphoid cells)¹ to receive more IL-2 signal.² This cascade of events leads to profound expansion of regulatory CD56^{bright} (NK cells). Daclizumab decreases immune responses by influencing T-cell priming by dendritic cells³ and by terminating the activation of autologous T cells by NK-mediated cytotoxicity.⁴ Strong correlations between CD56^{bright} NK-cell expansion and beneficial clinicoradiologic responses have been demonstrated, suggesting that this is a dominant mechanism of action of daclizumab in MS.^{4,5}

Daclizumab is generally well-tolerated; however, the safety profile of this agent is evolving and has yet to be fully characterized in phase 3 trials, making it important to recognize and report atypical daclizumab-related adverse events (AEs).

Herein, we report 3 patients with MS treated with daclizumab (Zenapax formulation [Roche Laboratories, Nutley, NJ], equivalent to daclizumab high-yield process) who developed AEs in various disparate organs: skin/hair follicles, lymphatic system, and breast tissue. These observed AEs were reversible or nonprogressive with medication discontinuation, and tissue biopsy was supportive of daclizumab-related effects. Although these observed AEs did not result in any serious adverse

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outcomes, they illustrate that daclizumab-related AEs can affect various organ systems and are AEs of which clinicians should be aware.

PATIENTS **Patient 1.** This 58-year-old man initially presented with myelopathy and diplopia. He fulfilled criteria for MS and initially had a mild disease course and declined disease-modifying therapy. However, after experiencing 2 relapses, he was started on daclizumab.

Twenty-four to 48 hours after his fourth daclizumab infusion, he developed a diffuse, pruritic, erythematous macular rash on his torso (figure 1). Over days, this rash became exfoliative and progressed to his face and limbs. Four to 6 weeks later, he noted hair loss of his scalp and eyebrows/eyelashes, which developed into alopecia universalis.

He discontinued daclizumab after rash onset and was treated with oral prednisone. The rash worsened and was accompanied by fever, leading to hospitalization and empiric treatment for cellulitis. Infectious and neoplastic workup was negative.

Punch skin biopsies of the hand/arm/thigh showed evidence of hyperkeratosis/parakeratosis, and necrotic keratinocytes. Perivascular lymphocytic infiltrates and lymphocytic exocytosis were present in the superficial dermis. There was no evidence of psoriasis, lymphoma, or pityriasis rubra pilaris. Although histologic findings were nonspecific, considering his clinical history, these findings seemed consistent with a drug eruption. He was treated with high-dose IV methylprednisolone followed by an oral prednisone taper. The rash gradually resolved over months. Hair follicle biopsies of the scalp and chin

Figure 1 Daclizumab-induced diffuse erythematous rash involving face, limbs, and torso of a patient

Daclizumab-induced diffuse erythematous rash involving face, limbs, and torso. (A, B) Initial rash manifestation. (C-F) Rash progression over 8 weeks.

performed 4 months after alopecia onset demonstrated lymphocytic infiltrates in the deep portions of the follicle. The alopecia was treated with cortisone injections and resolved 18 months after the last dose of daclizumab.

Patient 2. This 46-year-old man initially presented with myelopathic symptoms. Two years later, he developed paresthesias in his arms and was diagnosed with MS.

He started treatment with interferon β -1a (Avonex; Biogen Idec, Research Triangle Park, NC) but switched to high-dose interferon β -1a (Rebif; Merck, Darmstadt, Germany), then Rebif and mycophenolate mofetil (CellCept; Roche, Basel, Switzerland), and then daclizumab because of continuous disease activity. On daclizumab, he stabilized clinically and radiographically.

Forty-two months after starting daclizumab, he noticed an enlarged axillary lymph node, which was biopsied and reportedly benign. Seven months later, a routine MRI showed diffuse cervical and supraclavicular lymphadenopathy. He had no associated systemic symptoms/features.

A whole-body fluorodeoxyglucose (FDG)-PET with CT confirmed the presence of diffuse lymphadenopathy (figure 2A) with the largest node measuring 2.3 cm in the right axilla. There were also soft-tissue deposits in the right iliacus and psoas muscle.

He discontinued daclizumab and underwent another lymph node biopsy, which demonstrated T lymphocytes, B lymphocytes, and NK cells. There was no evidence of B-cell lymphoma.

A repeat FDG-PET scan 11 months later showed dramatic resolution of abnormal FDG-avid disease with either resolved or significantly decreased lymph

nodes on CT and no pathologically enlarged lymphadenopathy (figure 2B).

Patient 3. This 39-year-old woman was diagnosed with MS when she presented with imbalance and diplopia and a consistent MRI.

After diagnosis, she was enrolled in a study with an experimental agent (CGP77116: altered peptide-ligand) but discontinued it shortly after initiation because of an allergic reaction.

Two years after diagnosis, she started Avonex. She switched to Rebif 18 months later because of MS disease activity. On Rebif, she continued to have breakthrough disease; therefore, daclizumab was added. She tolerated this combination therapy, with clinicoradiographic stabilization.

Fifteen months after starting daclizumab, 3 well-circumscribed breast nodules were identified in the left breast on routine mammography/ultrasound; the largest measured 9.1×7.9 mm. These lesions were not observed on 3 prior mammograms performed 1, 3, and 5 years previously.

Tissue biopsy of 2 nodules revealed fragments of lymph nodes and fatty connective tissue without evidence of malignant cells and presence of CD20, CD4, CD8, and CD56 cells (figure 3).

She discontinued daclizumab when the breast nodules were identified. Follow-up mammogram 14 months after biopsy demonstrated stability in the nodules.

DISCUSSION Daclizumab is emerging as a novel therapeutic agent for the treatment of relapsing-remitting MS and has demonstrated efficacy in phase 2 clinical trials.^{5,6}

Figure 2 Diffuse lymphadenopathy in a patient treated with daclizumab and subsequent resolution following daclizumab discontinuation

(A) Fluorodeoxyglucose-PET scan demonstrating diffuse lymphadenopathy in a patient treated with daclizumab. (B) Resolution of lymphadenopathy after daclizumab discontinuation.

Figure 3 Immunohistochemistry of breast nodule of a patient treated with daclizumab

Immunohistochemistry of breast tissue demonstrating scattered CD56-positive cells.

Cutaneous events have been reported to occur with daclizumab (24% vs 6%; daclizumab vs placebo in CHOICE),⁵ along with lymphadenopathy.⁶ In this case series, we report daclizumab-related AEs in skin/hair follicles, breast tissue, and lymph nodes, illustrating that AEs related to daclizumab can affect various organs, and can manifest as early or late AEs after treatment initiation. To our knowledge, alopecia universalis and breast nodules in the context of daclizumab treatment have not yet been reported, and are noteworthy. In fact, alopecia may be a manifestation of a severe cutaneous AE. Reports of lymphadenopathy and cutaneous manifestations in previous daclizumab-treated cohorts and their resolution with daclizumab discontinuation in our series present a strong argument for a causal relationship. Although the exact mechanisms of lymphadenopathy with daclizumab are unknown, daclizumab facilitates proliferation of CD56^{bright} NK cells² and their differentiation from common innate lymphoid cell precursors.¹ Both of these processes likely occur in the lymphoid tissue⁷ and may be causally related to daclizumab-induced lymphadenopathy. However, because both processes are fully reversible after daclizumab discontinuation,⁸ the observed lack of regression of breast nodules raises the possibility that they were unrelated to daclizumab.

Reassuringly, the observed AEs did not result in serious adverse outcomes. Nonetheless, these AEs are important for clinician awareness, because progressive lymphadenopathy and breast nodules without another plausible etiology necessitate an aggressive workup for underlying malignancy, which can result in patient exposure to unnecessary radiation.

Although not considered serious AEs, severe cutaneous manifestations and alopecia universalis have

significant cosmetic repercussions and will need to be taken into risk/benefit consideration when making treatment decisions in patients with MS.

Although daclizumab was generally well-tolerated in a number of phase 2 studies,^{5,6} its AE profile is still evolving, and ongoing phase 3 studies will be informative in this regard. Of note, serious AEs, including serious infections/cutaneous events, and elevations in liver enzymes >5 times normal were observed more frequently with daclizumab vs placebo in phase 2 trials.^{5,6} In SELECT, one daclizumab-treated patient recovering from a rash died of a psoas abscess, but this AE was likely indirectly related to daclizumab, as it resulted from local arterial compression leading to mesenteric ischemia.⁶ In the extension phase of SELECT, one patient in the daclizumab 300-mg washout group died of autoimmune hepatitis (before implementation of hepatic-monitoring guidelines).⁹ There was a single case of CNS vasculitis in an open-label trial of daclizumab.¹⁰

The expanding treatment options for relapsing-remitting MS will make long-term safety and tolerability of emerging disease-modifying therapies one of the most important considerations in treatment selection. Our case series illustrates that daclizumab-induced AEs can affect a number of organs, sometimes even after prolonged exposure. These observations reinforce the need for continued surveillance and reporting of medication-induced AEs for novel pharmacologic agents. Further studies are needed to better characterize daclizumab-induced AEs in various organs and their relationship to CD56^{bright} NK-cell biology.

AUTHOR CONTRIBUTIONS

Conceptualization of the study: Jiwon Oh, Scott Newsome. Data collection: Jiwon Oh, Irene Cortese, Joan Ohayon, Bibiana Bielekova, Peter Calabresi, Scott Newsome. Analysis/interpretation of the data: Jiwon Oh, Shiv Saidha, Joan Ohayon, Bibiana Bielekova, Peter Calabresi, Scott Newsome. Drafting/revising the manuscript: Jiwon Oh, Shiv Saidha, Joan Ohayon, Bibiana Bielekova, Peter Calabresi, Scott Newsome.

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REFERENCES

1. Perry JS, Han S, Xu Q, et al. Inhibition of LT α cell development by CD25 blockade is associated with decreased intrathecal inflammation in multiple sclerosis. *Sci Transl Med* 2012;4:145ra106.
2. Martin JF, Perry JS, Jakhete NR, Wang X, Bielekova B. An IL-2 paradox: blocking CD25 on T cells induces IL-2-driven activation of CD56(bright) NK cells. *J Immunol* 2010;185:1311–1320.
3. Wuest SC, Edwan JH, Martin JF, et al. A role for interleukin-2 trans-presentation in dendritic cell-mediated T cell activation in humans, as revealed by daclizumab therapy. *Nat Med* 2011;17:604–609.
4. Bielekova B, Caltafamo M, Reichert-Scrivner S, et al. Regulatory CD56(bright) natural killer cells mediate immunomodulatory effects of IL-2 α -targeted therapy (daclizumab) in multiple sclerosis. *Proc Natl Acad Sci USA* 2006;103:5941–5946.
5. Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE Study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. *Lancet Neurol* 2010;9:381–390.
6. Gold R, Giovannoni G, Selmaj K, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. *Lancet* 2013;381:2167–2175.
7. Freud AG, Becknell B, Roychowdhury S, et al. A human CD34(+) subset resides in lymph nodes and differentiates into CD56bright natural killer cells. *Immunity* 2005;22:295–304.
8. Bielekova B. Daclizumab therapy for multiple sclerosis. *Neurotherapeutics* 2013;10:55–67.
9. Giovannoni GG, Gold R, Selmaj K, et al. Primary results of the SELECTION trial of daclizumab HYP in relapsing multiple sclerosis. Presented at the 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; October 13, 2012; Lyon, France.
10. Bielekova B, Becker BL. Monoclonal antibodies in MS: mechanisms of action. *Neurology* 2010;74(suppl 1):S31–S40.

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