

DRESS Syndrome and Daclizumab Failure—Were Potentially Dangerous Signs Missed in Clinical Trials?

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Drug Target Insights
Volume 12: 1–2
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DOI: 10.1177/1177392818785136



ABSTRACT: The US Food and Drug Administration (FDA) approved Zinbryta, an interleukin-2 receptor blocking antibody (daclizumab; Biogen and AbbVie) for the treatment of adults with relapsing forms of multiple sclerosis (MS) in May, 2016. It was also approved by the European Union in July, 2016. Zinbryta is a long-acting, self-administered monthly injection that was branded as a new MS drug for patients who needed a “new option for treatment.” It blocks interleukin-2 receptor alpha (CD25) and modulates T-cell expansion. The drug was withdrawn from the market in March, 2018 following 12 reports from Germany (9), United States (2), and Spain (1) following the development of “inflammatory encephalitis and meningoencephalitis” in patients on Zinbryta. Although cases of hepatotoxicity made news with Zinbryta earlier along this drug’s postmarketing journey in the treatment of patients with MS, the European Medicines Agency (EMA) ordered a review of the risks of hepatotoxicity with Zinbryta use June, 2017; this analysis will focus on the pharmacovigilance data concerning the central nervous system (CNS) complications. The details of the CNS complications have been elucidated by EMA. Every drug failure provides an opportunity for learning, but it is also noteworthy that no FDA-approved MS drug in modern times has met with such an untimely, sudden, and inglorious exit. This should serve as a cautionary tale for all clinicians who use “newer MS drugs” that have mushroomed in recent memory following a flurry of recent FDA approvals.

KEYWORDS: Daclizumab, DRESS syndrome, encephalitis, meningoencephalitis, CNS toxicity, drug trials

RECEIVED: March 27, 2018. **ACCEPTED:** June 4, 2018.

TYPE: Perspective

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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During the drug review process, as noted in the Center for Drug Evaluation and Research (CDER, <https://www.access-data.fda.gov/scripts/cder/daf/index.cfm>), one of the reviewers found that the drug caused microglial aggregates throughout the brain and spinal cord of study animals (cynomolgus monkeys), albeit a nonclinical finding, and recommended nonapproval for clinical use. While the biological significance of this finding, particularly as it relates to the dosing (7-fold safety margin at the 150-mg dose), at which the drug was studied remains unclear, it must be noted that microglial aggregates did not cause neuronal degeneration, axonal fragmentation, or demyelination. The drug was subsequently approved.

The black-box warning for Zinbryta package insert did note that, across all clinical trials, serious drug-related hepatic injury occurred in 1.7% of Zinbryta-treated patients. Furthermore, 5% of patients on Zinbryta developed serious immune-mediated disorders including skin reactions and lymphadenopathy. Across all clinical studies, immune-mediated disorders occurred in 28% of patients on Zinbryta, including skin reactions and lymphadenopathy. Some patients required invasive procedures for diagnosis and some patients did not improve even after stopping Zinbryta. Curiously, no cases of inflammatory encephalitis or meningoencephalitis were noted, however, but a safety and tolerability study did mention Drug Reaction with Eosinophilia and Systemic Symptoms or DRESS syndrome as a complication.¹ However, DRESS syndrome which is a purely clinical event will only be recognized if clinicians are alert to the possibility and are trained to recognize such events and not relegate them to an “MS relapse.”

As there is no established method to revisit data sets from clinical trials unless drug companies themselves put out such information in the face of drug being pulled from the market, that particular piece of information will forever be lost.

The EMA document published on March 6, 2018, notes that 4 patients developed skin rash and involvement of other organs including eosinophilia, whereas 5 other patients developed multi-organ failure probably related to immune-mediated phenomena. Specifically, none of these cases were initially identified as secondary to side effects of the drug; later, they were recognized as (DRESS) a conclusion that could have major ramifications on safety, and how data are interpreted by clinicians both in the clinical trials and developmental stages of the drug as well as in phase 4 use of the drug after approval. It is equally strange that no cases of encephalitis or meningoencephalitis were noted in the clinical trials and whether signs and symptoms were erroneously missed or misclassified as clinical worsening of MS remains a worry. If this is the case, the signs are ominous for future drug development strategies. In general, the phenomenon of “MS relapse” remains a major concern even in routine clinical assessment of patients with MS on medications. Patients are unlikely to be told that their findings are “drug related” and more likely told that their disease is worsening. It is important to note that almost all the cases described by the EMA led to pulling Zinbryta off the market, and the initial assessment was largely attributed to “worsening MS disease.” The mishap with Zinbryta ought to be a warning call to all clinicians to revisit definitions of what represents an MS relapse or clinical worsening and when to seek alternative explanations for “MS relapse.”



Hematologic abnormalities
Eosinophilia >1500/mm ³
Presence of atypical lymphocytes
Systemic involvement
Adenopathies >2 cm in diameter
Cytolytic hepatitis
Interstitial nephritis
Interstitial pneumonitis
Myocarditis

Figure 1. Salient features of DRESS syndrome, typically seen in the context of fever and skin rash.

The case report (n = 12) concerning the central nervous system (CNS) complications resulting from Zinbryta use in patients with MS was reported by the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA, which include 9 from Germany, 2 from the United States, and 1 from Spain, and published on March 6, 2018 (article 20 of regulation EC # 726/2004, pharmacovigilance data). The predominant clinical finding in most of the cases that led to the CNS complications was from DRESS syndrome (cases 1, 2, 6, 12, and probably case 3), whereas some cases had anti-NMDA encephalitis. The Zinbryta dosing for the cases labeled 1 through 5 included the following: 2, 4, 2, 2, and 8, respectively (doses given to each patient prior to clinical worsening attributed to DRESS syndrome). The pertinent findings for this case cluster included the following—exanthematous skin rash, fever, altered mental status, peripheral eosinophilia (9.3% that increased to 25.5% in case 1, 11.4% for case 2), and “MS relapse” characterized by clinical and radiological worsening. Brain biopsies, where performed, showed T- and B-cell infiltration, as well as plasma cell and eosinophilic granulocytes. In all, at least 3 patients died, in the reported cohort.

DRESS syndrome or drug reaction with eosinophilia and systemic symptoms is a life-threatening disease with cutaneous manifestations and internal organ involvement²; it carries a mortality rate of approximately 10%. The time of symptom onset varies, following drug exposure, and can be between 2 and 8 weeks. The incidence is unclear and overall population risk varies between 1 in 1000 and 1 in 10000 drug exposures.^{3,4} In general, DRESS syndrome is probably missed or overlooked owing to its varied presentation and a lack of understanding of its manifestations among physicians. Typical features of DRESS syndrome (Figure 1) include fever, widespread cutaneous lesions, eosinophilia,⁵ and atypical lymphocytosis,⁶ as well

as hepatic injury,² lymphadenopathy, and renal failure.² Additional organ involvement includes lung,² cardiac,⁷ and CNS involvement characterized as meningitis or encephalitis.⁸ Therefore, familiarity with the clinical features help clinicians pinpoint the diagnosis, and further worsening of symptoms can be mitigated by discontinuation of the offending agent. Sometimes this may be difficult if multiple drugs are used but understanding of triggers, time course, and clinical manifestations including dermal, internal organ, and laboratory abnormalities can help nail the diagnosis.

Viral reactivation, particularly HHV-6 reactivation, is thought to play an important role in DRESS syndrome, as seen in valproic acid use, for example.⁹ In addition, whether the patients who developed DRESS syndrome in the cohort of patients with MS also had other increased risk factors such as HLA class II alleles would be worth exploring. Many studies have reported DRESS syndrome patients with genetic predisposition linked to specific drugs and one wonders if Zinbryta use, DRESS syndrome, and HLA class II alleles were linked as well.

Author Contributions

JA is the sole author, therefore, the concept, analysis, layout and presentation is all done by JA.

REFERENCES

- Giovannoni G, Kappos L, Gold R, et al. Safety and tolerability profile of daclizumab in patients with relapsing-remitting multiple sclerosis: an integrated analysis of clinical studies. *Mult Scler Relat Dis*. 2016;9:36–46.
- Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms. A retrospective study of 60 cases. *Arch Dermatol*. 2010;146:1373–1379.
- Chiou CC, Yang LC, Hung SI, et al. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. *J Eur Acad Dermatol Venerol*. 2008;22:1044–1049.
- Shiohara T, Kano Y. Review of drug-induced hypersensitivity: special emphasis on drug-induced hypersensitivity syndrome. *Expert Dermatol*. 2012;7:539–547.
- Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. *Am J Med*. 2011;124:588–597.
- Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol*. 2013;169:1071–1080.
- Bourgeois GP, Cafardi JA, Groysman V, Pamboukian SV, Kirklin JK, Andea AA. Fulminant myocarditis as a late sequela of DRESS: two cases. *J Am Acad Dermatol*. 2011;65:889–890.
- Husain Z, Reddy BY, Schwartz RA. DRESS syndrome part 1. Clinical perspectives. *J Am Acad Dermatol*. 2013;68:693e1–639e14.
- Mardivirin L, Lacroix AD, Descamps V, Ranger-Rogez S. Augmentation de la replication in vitro de l'herpesvirus humain 6 en presence de valproate de sodium. *Virologie*. 2007;11:1–3.