

A fatal case of daclizumab-induced liver failure in a patient with MS

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Daclizumab (DAC; Zinbryta) is a humanized monoclonal antibody directed against the IL-2 receptor alpha chain and was approved for treatment of relapsing-remitting MS (RRMS) in May 2016. In March 2018, DAC has been withdrawn from the market, after the fatal case of severe liver failure described here and 12 other cases (3 of them fatal) of serious inflammatory brain disorders including encephalitis and meningoencephalitis. Notably, most of the cases occurred in Germany,^{1–4} most likely because DAC received only a third-line approval by the US Food and Drug Administration.

Here, we present the fatal case of a 26-year-old woman with severe liver failure after a 4-month therapy with DAC that had been initiated 5 months after the first diagnosis of RRMS during which the patient presented severe and unusually high disease activity (expanded disability status scale [EDSS] score of 5.5). On first diagnosis, the presence of thyroid peroxidase (92 U/L) and thyroglobulin antibodies indicated a comorbidity with Hashimoto disease. Although liver enzyme counts including aspartate transaminase (AST, 42 U/L) and alanine transaminase (ALT, 84 U/L) doubled within the 2.5 weeks prior DAC initiation, values normalized prior to first administration of the drug and remained stable during the treatment. A decreased EDSS score of 4.5, assessed after 4 months, confirmed the patient's response to treatment.

Three weeks after receiving the fourth dose of DAC, the patient developed fatigue and jaundice with significantly increased AST (3,041 U/L; reference <35 U/L), ALT (4,760 U/L; reference <35 U/L), lactate dehydrogenase (628 U/L; reference <215 U/L), and total bilirubin (21.5 mg/dL; reference <1.1 mg/dL) values. Two days later, she was hospitalized in a somnolent state with jaundice, arterial hypotension, and lactate acidosis. Diagnosis of acute irreversible liver failure prompted a high urgency liver transplantation that was performed the following day, after receiving approval by the ELAC (Eurotransplant Liver Advisory Committee) audit. One day after transplantation, the patient developed circulatory instability and catecholamine dependency with continuous peaks of transaminases (AST: 8,568 U/L; ALT: 4,207 U/L). Despite intensified treatment, the patient died 4 days later because of systemic inflammatory response syndrome, septic shock, and multiple organ failure.

We suspected DAC-induced hepatic (DIH) injury possibly owing to natural killer (NK)-cell hyperactivation, because drug reaction with eosinophilia and systemic symptoms (DRESS) and other causes of hepatic injury, including alcohol and drug abuse or viral hepatitis, could be excluded. A contribution of tizanidine, which was administered as co-medication after the fourth cycle of DAC treatment and has also been shown to induce serious liver injury as

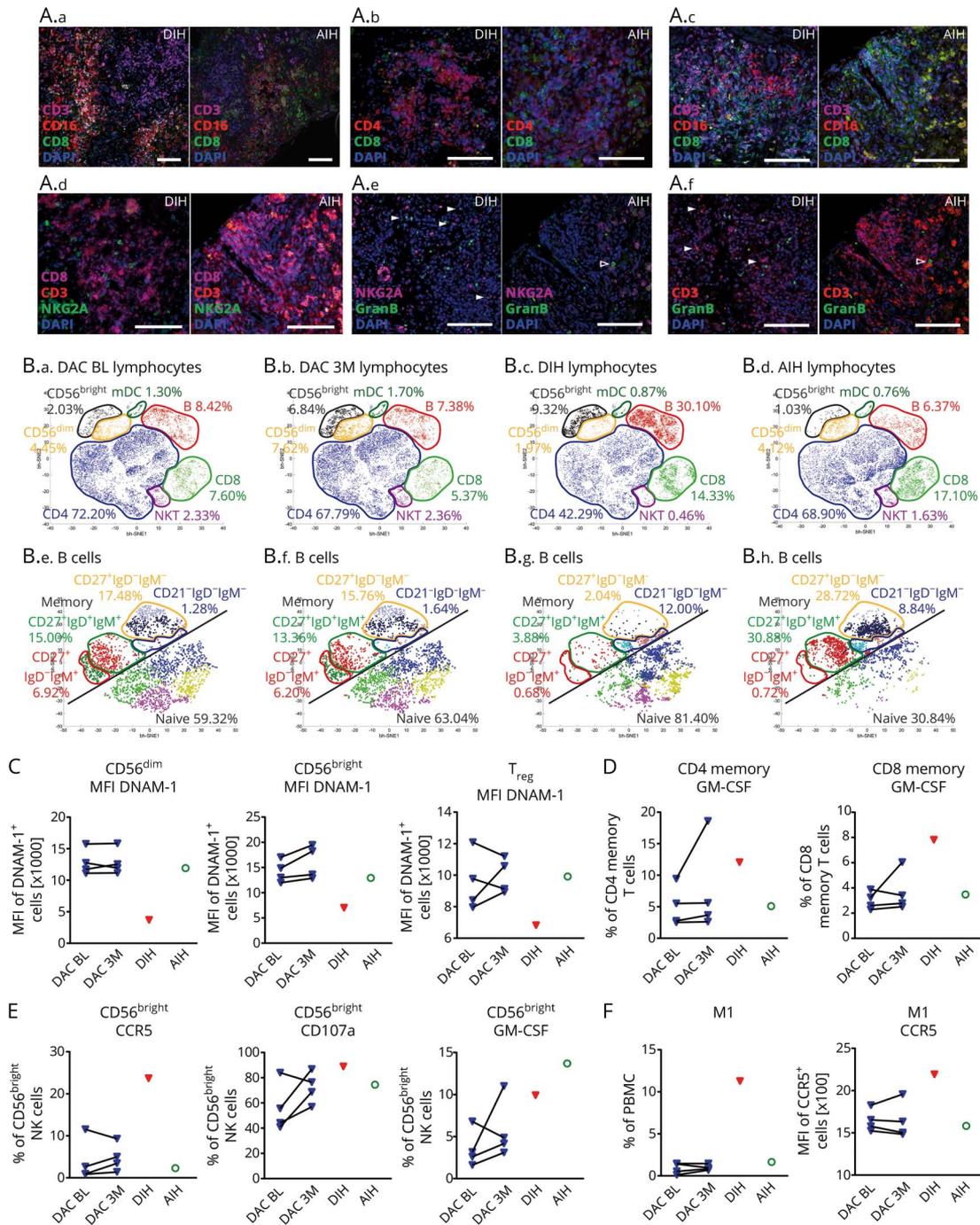
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(A) Immunohistochemical detection of leukocyte infiltration in the liver of the fatal case patient with DAC-induced hepatic injury (DIH) compared to the case of a 39-year-old RRMS patient with AIH but no further relevant medical conditions. At timepoint of biopsy, this patient received glatiramer acetate without any further relevant co-medications. Seven-micrometer paraffin embedded sections were stained, with anti-CD16 (macrophages, neutrophils, NK cells), anti-CD3 (T cells), anti-CD4 (T-helper cells), anti-CD8 (cytotoxic T cells), anti-NKG2A (NK cells), anti-CD19 (B cells), and granzyme B (GranB) and matching fluorochrome-labeled secondary antibodies (Alexa Fluor 488, green; Alexa Fluor 555, red; Alexa Fluor 647, purple) as indicated; nuclei were visualized using 4,6'-diamidino-2-phenylindole (DAPI, blue); scale bar 100 μ m. (A.a) Representative image of CD16⁺ macrophages localized around T-cell infiltration zones. (A.b) Distribution of CD4⁺ T-helper cells and cytotoxic CD8⁺ T cells within T-cell infiltrates. (A.c) CD19⁺ B cells within T-cell infiltration zone. (A.d) NKG2A + CD3⁺ NK cells within T-cell infiltration zone. (A.e and A.f) Granzyme B expression of NKG2A + NK cells (A.e) and CD3⁺ T cells (A.f) on Sequential sections. (B) PBMC derived from patients with MS (N = 4) before (DAC BL [B.a]) and after 3 months of DAC therapy (DAC 3M [B.b]) in comparison to the index case (DIH [B.c]) as well as the patient with autoimmune hepatitis (AIH [B.d]) were stained with lineage-specific (B.a–B.d) CD1c, CD3, CD4, CD8, CD14, CD16, CD19, CD56) and B-cell subset-specific (B.e–B.h) CD19, CD20, CD21, CD23, CD24, CD27, CD38, IgD, IgM) fluorochrome-conjugated antibodies and acquired by flow cytometry. Lymphocytes and B cells were electronically selected and resulting data were normalized before submitting equal numbers of randomly selected cells to unsupervised cluster analysis by viSNE software. Barnes–Hut Stochastic Neighbor Embedding (bh-SNE) algorithm was used for dimensionality reduction followed by automated identification of lymphocyte (B.a–B.d) and B-cell subsets (B.e–B.h), respectively, by phenograph algorithm. (C) Median fluorescence intensity (MFI) of DNAM-1 expressing CD56dim, CD56bright, and regulatory T cells (Treg). (D) Intracellular expression of GM-CSF in CD4 and CD8 memory T cells following stimulation with leukocyte activation cocktail (PMA, ionomycin, brefeldin A). (E) Percentage of CD56bright NK cells expressing CCR5, or secreting cytolytic vesicles (CD107a+), and expressing GM-CSF as a consequence of co-incubation with HepG2 liver cells. (F) Proportion and MFI of CCR5 of monocytes with a proinflammatory M1-like phenotype.

a monotherapy,^{5,6} could not be excluded. Interestingly, tizanidine was the common denominator between this case and another fatal case of DIH injury in the SELECT trial.^{5,7}

Immunohistochemistry of the explanted liver tissue of the patient with DIH revealed CD3⁺ T-cell infiltrates surrounded by damaged zones of CD16⁺ macrophages. The same observations were made for the liver tissue of a 39-year-old woman diagnosed with autoimmune hepatitis (AIH) 7 months after first diagnosis of MS (figure 1A) as an example of an autoinflammatory disease of both CNS and liver. While CD4⁺ T-helper cells dominated in the patient with DIH, equal numbers of T-helper and cytotoxic CD8⁺ T cells were observed in the AIH liver tissue. Despite the fact that autoimmune liver disease has a wide pathophysiologic spectrum, more B-cell infiltrates were detected within the T-cell zones of the patient with DIH compared to AIH. Enrichment of granzyme B-expressing NKG2A⁺ NK-cells in the DIH liver tissue suggests an active role of NK cells in hepatic injury.

In accordance with enriched B-cell infiltrates in the DIH liver, immune cell profiling of the blood revealed significantly enhanced circulating B cells (figure 1B), consisting mainly of naive B cells and increased proportions of autoreactive antibody expressing complement receptor (CD21) negative B cells.⁸ Despite a DAC-induced increase of CD56^{bright} NK cells, the DIH case exhibited significantly decreased proportions of CD56^{dim} NK cells.^{9,10} Diminished cell-surface expression of the activating receptor DNAM-1 (DNAX Accessory Molecule-1), which has been recently identified as a crucial player in NK- and regulatory T(T_{reg})-cell mediated control of T-cell activity, on NK⁶ and T_{reg}⁷ (figure 1C), suggests impaired immune regulatory function. Accordingly, proinflammatory granulocyte-macrophage colony-stimulating factor (GM-CSF) production was increased in circulating T cells of the patient with DIH (figure 1D). Increased expression of the liver homing receptor C-C chemokine receptor type 5 (CCR5) on CD56^{bright} NK cells and enhanced cytotoxic function as well as GM-CSF production in response to liver cells (figure 1E) indicated expanded liver invasion and hepatotoxicity of this subset. Finally, enhanced GM-CSF levels resulting from T- and NK-cell hyperactivation may drive the differentiation of CCR5-expressing proinflammatory M1-like monocytes leading to the highly increased frequencies observed in the blood of the patient with DIH (figure 1F).¹¹ Overall, our findings indicate DIH injury resulting from innate immune cell activation and impaired immune regulation. Although involvement of the liver frequently occurs in DRESS, this case does not fulfill critical criteria for DRESS such as hyper-eosinophilia, rashes, and reactivation of herpes viruses,^{12,13} thus, differing from the recently described DAC-induced DRESS cases.

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Disclosure

M. Stettner served on the scientific advisory board for UCB and Biogen Idec; received travel funding and/or speaker honoraria from Biogen, Genzyme, Novartis, Sanofi-Aventis, UCB, Grifols, TEVA, and Bayer; and served as an associate editor for *European Journal of Medical Research*. C.C. Gross received speaker honoraria and travel funding from Biogen, Euroimmun, Genzyme, Mylan, Novartis, and Bayer; served as review editor for *Frontiers in Neuroimmunology*; and received research support from ReSTORE German Research Foundation, BMFB, and Innovative Medical Science. A.K. Mausberg reports no disclosures. R. Pul served on the scientific advisory board for Merck, Biogen, Bayer, and Novartis; received travel funding and/or speaker honoraria from Merck, Biogen, Mylan, TEVA, and Sanofi-Genzyme; served as guest editor for *Frontiers in Neurology, Cells*; and received research support for TEVA, Novartis, Merck, Sanofi-Genzyme. A. Junker, H.A. Baba, and A. Schulte-Mecklenbeck report no disclosures. H. Wiendl served on the scientific advisory board for Bayer, Biogen, Sanofi-Genzyme, Merck Serono, Novartis, Roche, and TEVA; received travel funding and/or speaker honoraria from Bayer Vita, Bayer Schering, Bioven, CSL Behring, EMD Serono, Fresenius Medical Care, Sanofi-Genzyme, Merck Serono, Omni-Mad, Novartis, TEVA, GlaxoSmithKline, and GW; served as an editorial board member for *PLoS One, Neurotherapeutics, Recent Patents on Inflammation & Allergy Drug Discovery*; consulted for Biogen, Merck Serono, Novartis, OmniaMed, Roche, and Sanofi-Genzyme; and received research support from Bayer HealthCare, Bayer Vital, Biogen, Merck Serono, Novartis, Sanofi-Genzyme, Sanofi, TEVA, German Ministry for Education and Research, Interdisciplinary Centre of Clinical Research, PML Consortium, German Research Foundation, Else Kröner-Fresenius Foundation, Hertie Foundation, RE Children's Foundation. C. Kleinschnitz receives honoraria for lecturing and travel expenses for attending meeting from Amgen, Bayer HealthCare, Bristol-Myers Squibb, Boehringer Ingelheim, Biogen, Biotronik, CSL Behring, Daiichi Sankyo Genzyme, Desitin, Eisai, Ever Pharma, MedDay Pharmaceuticals, Merck Serono, Mylan, Novartis, Pfizer, Roche, Sanofi-Aventis, Siemens, Stago, and Teva; received research funding from the German Ministry for Education and Research (BMBF), Corona Foundation, Deutsche

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Appendix 1 Author contributions

Name	Location	Role	Contribution
Mark Stettner	Department of Neurology, University Hospital Essen, Essen, Germany	Author	Designed and conceptualized the study; analyzed and interpreted data; and drafted the manuscript for intellectual content
Catharina C. Gross	Clinic of Neurology, University Hospital Münster, Münster, Germany	Author	Designed the study; analyzed and interpreted data; and drafted the manuscript for intellectual content
Anne K. Mausberg	Department of Neurology, University Hospital Essen, Essen, Germany	Author	Played a major role in the acquisition and interpretation of data
Refik Pul	Department of Neurology, University Hospital Essen, Essen, Germany	Author	Designed the study; played a major role in the acquisition of data; and revised the manuscript
Andreas Junker	Institute of Neuropathology, University Hospital Essen, Essen, Germany	Author	Played a major role in the acquisition of data and revision of the manuscript
Hideo A. Baba	Institute of Pathology, University Hospital Essen, Essen, Germany	Author	Played a major role in the acquisition of data and revision of the manuscript
Andreas Schulte-Mecklenbeck	Clinic of Neurology, University Hospital Münster, Münster, Germany	Author	Played a major role in the experimental design, acquisition, and analysis of flow cytometry data; designed figures; and revised the manuscript
Heinz Wiendl	Clinic of Neurology, University Hospital Münster, Münster, Germany	Author	Interpreted data and revised the manuscript for intellectual content
Christoph Kleinschnitz	Department of Neurology, University Hospital Essen, Essen, Germany	Author	Designed the study; analyzed and interpreted data; and drafted the manuscript for intellectual content
Sven G. Meuth	Clinic of Neurology, University Hospital Münster, Münster, Germany	Author	Conceptualized the study; analyzed and interpreted data; and drafted the manuscript for intellectual content

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