Journal Club:

Intrathecal effects of daclizumab treatment of multiple sclerosis

Raphael Schneider, MD
Nathalie Arbour, PhD

Correspondence & reprint
requests to Dr. Schneider:
raphael.schneider@utoronto.ca

The topic of this Journal Club is a study by Bielekova et al.,¹ who assessed whether daclizumab monotherapy reduces contrast-enhancing lesions (CEL) in patients with relapsing-remitting multiple sclerosis (RRMS). Furthermore, they evaluated the effects of daclizumab on clinical outcome measures and on NK cell populations in the CSF and blood of treated patients.

BACKGROUND AND SIGNIFICANCE Multiple sclerosis (MS) is an immune-mediated disease of the CNS characterized by demyelination and axonal loss.² Although the etiology of the disease is still unknown, aberrant activation of T and B cells is believed to play a central role in the pathophysiology of MS.^{2,3} One of the recent strategies to try to modulate the immune system is treatment with daclizumab, a humanized antibody directed against CD25, which is the interleukin (IL)-2 receptor α -chain (IL-2R α). In association with CD122 and the common γ chain, CD25 forms a high-affinity receptor for IL-2. While resting T cells express low levels of CD25, activated T cells upregulate its expression and are thus susceptible to IL-2 signaling. Since IL-2 promotes survival of T cells, it was predicted that blocking CD25 with daclizumab would selectively inhibit activated T cells. Recent studies showed that daclizumab can mediate its effects through various mechanisms of action. It can inhibit antigen-specific T-cell responses through blockage of CD25 on dendritic cells (DCs).⁴ In addition, daclizumab can expand CD56^{bright} natural killer cells (NK cells). CD56^{bright} NK cells express a high surface density of CD56 on flow cytometry and can regulate T-cell responses.^{5,6} Conversely, CD56^{dim} cells express less CD56 and have a more cytotoxic phenotype.

A recent phase II trial of daclizumab in patients with relapsing-remitting MS (RRMS) with incomplete response to interferon (IFN)- β showed a signif-

icant reduction in the number of new or enlarged CEL on brain MRI (CHOICE study).⁷ The investigators of the CHOICE study did not find significant changes in absolute numbers of T cells or B cells in the peripheral blood of treated patients. However, a post hoc analysis of all patients who received daclizumab treatment revealed that increased numbers of CD56^{bright} NK cell counts were associated with fewer new CEL during the treatment period. Given the promising results of the CHOICE study, Bielekova and colleagues investigated the efficacy and possible mechanisms of action of daclizumab as a first-line monotherapy.

HYPOTHESIS AND DESIGN What is the therapeutic efficacy of daclizumab monotherapy in patients with RRMS? Do CD56^{bright} NK cells expand intrathecally and if so, do they affect T- and B-cell populations or other mediators of inflammation? To answer these questions, Bielekova and colleagues performed a single-center, open-label, baseline vs treatment crossover phase II trial. The study population consisted of 16 patients with RRMS diagnosed with the 2001 McDonald criteria. Patients included scored between 1.0 and 5.5 on the Expanded Disability Status Scale (EDSS). Brain MRI showed a mean of ≥ 0.5 CEL per month during a baseline period of 12 weeks prior to treatment. All patients received IV daclizumab (1 mg/kg) at week 0 and 2, then every 4 weeks up to week 54. Clinical and brain MRI follow-up visits were scheduled once every month.

The primary endpoint of the study was reduction of new CEL from baseline to primary treatment phase (week 18 to 30). Secondary endpoints were reduction of new CEL from baseline to completion of treatment phase (weeks 42 to 54) and change in the Multiple Sclerosis Functional Composite (MSFC). Tertiary endpoint measures were as fol-

From the Department of Medicine (R.S.), Division of Neurology, University of Toronto, Toronto; and Department of Medicine (N.A.), Université de Montréal, CRCHUM, Montréal, Canada.

Study funding: Raphael Schneider received a postdoctoral fellowship from the Multiple Sclerosis Society of Canada. Nathalie Arbour holds a Donald Paty Career Development Award from the Multiple Sclerosis Society of Canada and is a Research Scholar from the Fonds de la Recherche en Santé du Québec.

Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this article.

lows: change in EDSS, Scripps Neurological Rating Scale (Scripps NRS), volume of CEL, T2 lesion volume, whole brain magnetization transfer ratio, brain fractional volume, and analysis of lymphocyte populations and soluble immune mediators between baseline and treatment phases in the peripheral blood and CSF.

METHODS Imaging. Contrast-enhanced T1-weighted MRI and T2-weighted and fluid-attenuation inversion recovery (FLAIR) images were obtained. To ensure analysis of the same volume of brain parenchyma images from the initial scans were compared to all subsequent examinations. Wilcoxon signed-rank test was used for statistical analyses.

Immunology. Blood samples were analyzed using flow cytometry. Lymphocyte surface markers were evaluated after osmotic lysis of red blood cells. A bead-based immunoassay was used to assess for IL-6, IL-7, IL-8, IL-10, IL-17, IL-12p40 (or p40) and p70, IL-21, IFN- γ , oncostatin M, tumor necrosis factor, lymphotoxin- α , vascular endothelial growth factor, CX3CL1, and granzyme B. IL-23 was measured by enzyme-linked immunoassay.

RESULTS Generally, daclizumab was well tolerated. However, the drug was stopped in 1 patient who developed palindromic rheumatism. Another patient dropped out of the study due to high disease activity during the baseline period of 12 weeks. As no response was seen after 3 doses of daclizumab, this patient was switched to more aggressive treatment. The trial achieved its primary outcome as the number of new CEL was significantly reduced after daclizumab treatment. In addition, the volume of CEL was found to be reduced. Similar results were obtained for the primary treatment phase and the completion of treatment phase. Significant improvement in the MSFC, the Scripps NRS, as well as the EDSS was observed as well. A nonsignificant decrease in relapse rate was noted. Immunologic studies were performed at baseline and in treatment week 26. Daclizumab did not alter lymphocyte counts within the CSF. NK cells were increased in the peripheral blood and CSF during daclizumab treatment and expansion of CD56^{bright} NK cells was observed in both compartments. Daclizumab treatment saturated the Tac epitope of CD25, which is essential for IL-2 binding, on both NK cells and CD4 T cells. Furthermore, intrathecal levels of IL-12p40, a common subunit of IL-12 and IL-23, decreased during daclizumab therapy. However, neither IL-12 nor IL-23 could be quantified.

INTERPRETATION In this study, Bielekova and colleagues provide compelling data in support of da-

clizumab as a monotherapy for the treatment of RRMS. Daclizumab reduced the number of CEL in patients with RRMS over a 54-week period and improved clinical features measured by MSFC and EDSS. This is consistent with the findings of earlier studies where daclizumab was used as an add-on therapy⁷ or as monotherapy in patients with persistent disease activity after IFN- β treatment.⁶ Although 2 patients dropped out, there were no opportunistic infections or deaths over the course of the present study. Unselective depletion of immune cells from the CNS can put patients at risk of developing progressive multifocal leukoencephalopathy (PML).⁸ Daclizumab did not seem to block access of immune cells into the CNS. Instead, it increased the number of regulatory CD56^{bright} NK cells in the peripheral blood and the CSF of treated patients. Hence, daclizumab had a direct or indirect impact on the NK cell population within the CNS shifting the balance toward an anti-inflammatory immune response. Of note, no case of PML after daclizumab treatment has been reported so far. These preliminary results indicate that daclizumab may have the potential to improve the risk–benefit ratio when compared to already available therapies such as natalizumab.

There are, however, some limitations of this study.

Limited size and duration of the study. Only 15 patients completed the study. Treated patients were followed for only 1 year.

The authors used appropriate statistical analyses for all outcome measures of this relatively small study. However, larger studies of longer duration are required to confirm the clinical efficacy of daclizumab and determine the number needed to treat to achieve clinical improvement. Importantly, the time required for daclizumab to reach its full therapeutic effect may be even outside the study period.

Study of a subgroup of patients with MS. Only patients with RRMS were included. Most patients presented with mild physical disability.

Although most patients with MS present initially with a relapsing-remitting disease course,² patients with more progressive forms of MS will have to be included in future studies. The EDSS of patients in the beginning of this study were reported between 1.0 and 5.5, yet the median EDSS was well below 2. Thus, the patient population studied here underrepresents the full spectrum of the disease. Moreover, the 2001 McDonald criteria were used to include patients into this trial. With new diagnostic criteria emerging, it is essential to reproduce the results shown here in an MS population diagnosed with criteria currently in use.⁹

Open-label design without placebo control. As new and effective agents for the treatment of MS emerge, it is becoming more problematic to conduct randomized and placebo-controlled studies. Unfortunately, knowledge about being on an active drug may impact reporting of outcomes in open trials. Therefore, improvement in clinical scales like the MSFC, the Scripps NRS, as well as the EDSS has to be interpreted with caution.

Technical difficulties to assess the intrathecal immune system. Daclizumab strikingly decreased IL-12p40 (or p40) levels in the CSF. P40 is a subunit of IL-12 and IL-23 and although less well studied, the p40 monomer as well as the p40₂ homodimer have been identified.³ Importantly, IL-12 and IL-23 are thought to play central roles in CD4 T cell polarization and phenotypic plasticity favoring either a Th1 or a Th17 response.¹⁰ Despite 10-fold concentration of CSF, measurements of most soluble mediators (13/16 tested) including IL-12 and IL-23 were below the detection limit of the assays used, suggesting that such CSF monitoring is not helpful as a measure of treatment efficacy. Hence, to assess the effect of daclizumab on these cytokines in future studies, analysis of peripheral blood could be more suitable.

In this study, Bielekova and colleagues did not assess DCs, the principal activators of T cells. It was recently proposed that DCs deliver IL-2 via CD25 to T cells in an immune synapse resulting in T cell expansion and development of antigen-specific T effector cells.⁴ Consequently, blocking CD25 on DCs with daclizumab would interfere with early T-cell activation.

Further investigations on how daclizumab treatment alters the complex cytokine network may provide a better understanding of its underlying mechanisms of action and possibly lead to a better understanding of MS pathophysiology.

AUTHOR CONTRIBUTIONS

Raphael Schneider: drafting/revising the manuscript, analysis or interpretation of data. Nathalie Arbour: drafting/revising the manuscript, analysis or interpretation of data.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

REFERENCES

1. Bielekova B, Richert N, Herman ML, et al. Intrathecal effects of daclizumab treatment of multiple sclerosis. *Neurology* 2011;77:1877–1886.
2. Sospedra M, Martin R. Immunology of multiple sclerosis. *Annu Rev Immunol* 2005;23:683–747.
3. Schneider R, Mohebiany AN, Ifergan I, et al. B cell-derived IL-15 enhances CD8 T cell cytotoxicity and is increased in multiple sclerosis patients. *J Immunol* 2011;187:4119–4128.
4. 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.
5. Bielekova B, Catalfamo M, Reichert-Scriver S, et al. Regulatory CD56(bright) natural killer cells mediate immunomodulatory effects of IL-2Ralpha-targeted therapy (daclizumab) in multiple sclerosis. *Proc Natl Acad Sci USA* 2006;103:5941–5946.
6. Bielekova B, Howard T, Packer AN, et al. Effect of anti-CD25 antibody daclizumab in the inhibition of inflammation and stabilization of disease progression in multiple sclerosis. *Arch Neurol* 2009;66:483–489.
7. 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.
8. Kappos L, Bates D, Edan G, et al. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. *Lancet Neurol* 2011;10:745–758.
9. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69:292–302.
10. Schneider R. T cells with commitment issues. *Sci Signal* 2010;3:jc3.

Neurology®

Journal Club: Intrathecal effects of daclizumab treatment of multiple sclerosis

Raphael Schneider and Nathalie Arbour

Neurology 2012;78:e131-e133

DOI 10.1212/WNL.0b013e31825830e3

This information is current as of May 28, 2012

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/78/22/e131.full
References	This article cites 10 articles, 4 of which you can access for free at: http://n.neurology.org/content/78/22/e131.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Immunology http://n.neurology.org/cgi/collection/all_immunology Autoimmune diseases http://n.neurology.org/cgi/collection/autoimmune_diseases MRI http://n.neurology.org/cgi/collection/mri Multiple sclerosis http://n.neurology.org/cgi/collection/multiple_sclerosis
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright Copyright © 2012 by AAN Enterprises, Inc.. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.