

IL-2 Receptor Inhibitor Reduced Lesions in MS

BY JEFF EVANS

Multiple sclerosis patients who experience relapsing disease while taking interferon beta might be able to reduce their number of new or enlarging lesions by adding the humanized monoclonal antibody daclizumab.

Besides reducing the risk of lesion growth and formation, the antibody might exert at least part of its effects through a mechanism that is now suggested by several lines of evidence to be a potential drug target and an important part of further understanding the pathogenesis of the disease, Dr. Daniel Wynn of Consultants in Neurology Multiple Sclerosis Center, Northbrook, Ill., and his associates reported (*Lancet Neurol.* 2010 Feb. 16 [doi:10.1016/S1474-4422(10)70033-8]).

Daclizumab (Zenapax) has been already approved by the Food and Drug Administration for the prophylaxis of acute organ rejection in patients receiving renal transplants.

"The true effects of this trial and previous observations on daclizumab might be more far-reaching than they seem at first glance," Dr. Olaf Stüve and Dr. Benjamin M. Greenberg wrote in an editorial (*Lancet Neurol.* 2010 Feb. 16 [doi:10.1016/S1474-4422(10)70032-6]).

Daclizumab was thought to inhibit T-cell proliferation and activation by binding to the CD25 subunit of the human high-affinity interleukin-2 receptor, but in this and other studies of MS patients treated with daclizumab, T cells have shown normal proliferative and activation responses.

Rather than reduce the activation or proliferation of T cells, Dr. Wynn and his colleagues found that the reduction of disease activity with daclizumab appears to be associated with an expansion of a regulatory subset of CD56^{bright} natural killer cells, which constitute only about 10% of all natural killer cells but is the predominant phenotype in the lymph nodes and tonsils.

In the 51-center CHOICE study, the investigators randomized 75 patients to daclizumab 2 mg/kg every 2 weeks, 78 patients to daclizumab 1 mg/kg every 4

VITALS

Major Finding: Patients taking 2 mg/kg of daclizumab every 2 weeks plus interferon beta had significantly fewer new or enlarged gadolinium-enhancing lesions after 24 weeks of treatment than did those taking interferon beta plus placebo (1.32 vs. 4.75).

Data Source: CHOICE study: Double-blind, randomized, placebo-controlled, phase II trial of 230 patients with active relapsing MS

Disclosures: Many investigators reported potential conflicts of interest with Biogen Idec Inc., maker of the MS medications, Tysabri and Avonex. Some of the investigators are employed by and own stock with either Biogen Idec or Facet Biotech Corp., both of which funded the trial. Dr. Greenberg and Dr. Stüve disclosed potential conflicts of interest with several manufacturers of MS drugs.

weeks, and 77 patients to placebo. These patients had a mean age of about 40 years and continued to take their baseline interferon beta regimens. Patients in each treatment arm averaged about 2.5 relapses in the previous 2 years and had a mean Expanded Disability Status Scale score of 3 (0 = normal; 10 = death). All of the patients had experienced at least one relapse or at least one gadolinium-enhancing brain or spinal cord lesion in the previous year while on a stable interferon beta regimen.

No significant differences were noted between the low-dose daclizumab and placebo groups on any of the imaging or clinical end points.

However, at 24 weeks, significantly fewer new or enlarged gadolinium-enhancing lesions had developed in the high-dose daclizumab group, compared with the placebo-treated group (mean of 1.32 lesions vs. 4.75, respectively). Enlarged lesions were defined by at least a 50% increase in size for lesions measuring at least 5 mm in diameter and by at least a 20% increase in size for lesions less than 5 mm.

High-dose daclizumab also was associated with a significantly lower number of new gadolinium-enhancing lesions alone, compared with placebo (mean of 1.18 vs. 3.95).

By 24 weeks, the high-dose daclizumab patients developed significantly fewer T2 lesions than did placebo-treated patients (1.1 vs. 3.4).

None of the groups were significantly different in terms of the change in their T1 hypointensities, the change in the vol-

ume of their T2 lesions, or their annualized relapse rate or mean time to relapse.

When daclizumab treatment was discontinued in a 48-week posttreatment period, the formation of lesions returned to about the same level in all groups.

In a post hoc analysis, higher counts of CD56^{bright} natural killer cells were associated with significantly fewer new gadolinium-enhancing lesions during the treatment period after adjusting for baseline gadolinium-enhancing lesions and

high-vs.-low daclizumab dosing.

Daclizumab-treated patients who were in the highest quartile of CD56^{bright} natural killer cell expansion at 20 weeks had 75% fewer new gadolinium-enhancing lesions than did those in the lowest quartile and 88% fewer than did those in the placebo group.

"Identifying the physiological mechanism or mechanisms that lead to the expansion of [CD56^{bright} natural killer cells] during disease remission might prove crucial in further understanding disease mechanisms and in developing novel therapeutics," wrote Dr. Stüve and Dr. Greenberg of the department of neurology at the University of Texas Southwestern Medical Center, Dallas.

Serious adverse events in patients treated with daclizumab most often consisted of infections and infestations, none of which were opportunistic or resulted in death. Two patients who received daclizumab developed malignant disease, one with breast cancer and one with a recurrence of pseudomyxoma peritonei. ■

Drug Is Good Candidate for Phase III

MY TAKE

In this phase II trial, treatment with high-dose daclizumab significantly reduced the number of gadolinium-enhancing lesions in MS patients, which suggests that it is a good candidate to move forward into phase III clinical trials. However, because the treatment phase of the trial lasted only 6 months, we cannot know yet what effect the drug has on the rate of relapse and other clinical measures.

It seems to be a reasonable approach to further study the use of daclizumab as an add-on therapy to interferon beta, but it will be important to know the full safety profile of daclizumab when used with other MS therapies. Progressive multifocal leukoencephalopathy has been as-

sociated with other monoclonal antibodies such as natalizumab (Tysabri) and rituximab (Rituxan), especially when used in combination with other immunomodulating or immunosuppressive agents.

Daclizumab did not seem to have a worrisome side effect profile, but some patients developed a skin rash, particularly those in the group that was given low-dose daclizumab.



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Neutralizing Antibodies to Interferon Beta May Worsen MS

BY MARY ANN MOON

Neutralizing antibodies to interferon beta not only persist in some multiple sclerosis patients who discontinue the recombinant-DNA treatment, they also appear to worsen the disease course.

In patients with relapsing-remitting MS who had been treated with interferon beta in the past, the relapse rate was higher and progression of disability faster in those who had neutralizing antibodies in their circulation than in those who did

not have the antibodies, said Dr. Laura F. van der Voort of Vrije University Medical Center, Amsterdam, and associates.

They reviewed the medical records of 71 MS patients treated with interferon beta between 1994 and 2006. A median of 25 months after discontinuing therapy, 17 patients (24%) still had circulating neutralizing antibodies to interferon beta.

Patients with persistent antibodies were no different from those without them, even when considering potential predisposing factors such as age at MS on-

set, sex, MS subtype, disease duration, duration of interferon-beta therapy, and degree of disability at the start of treatment. The relapse rate was nearly 5 times higher in antibody-positive patients than in antibody-negative patients (*Arch. Neurol.* 2010; Feb. 8 [doi:10.1001/archneurol.2010.21]).

Patients with persistent neutralizing antibodies also showed faster progression of disability when evaluated using the Expanded Disability Status Scale.

"Most patients who discontinued interferon beta treatment be-

cause of perceived efficacy failure were not neutralizing-antibody positive," the authors wrote. It is not yet clear why neutralizing antibodies to interferon beta can persist months or years after exposure to the antigen has ceased or how persisting antibodies exert their effect on MS activity.

It is possible that the antibodies affect endogenous interferon pathways, causing "a more proinflammatory modification of the immune system. Alternatively, the tendency to develop and sustain anti-interferon beta antibodies might be a reflection of a

more active immune system."

The retrospective nature and the small sample of the study did not allow for definitive conclusions to be drawn, and causality could not be proven, they added.

This study was supported in part by a targeted research project on neutralizing antibodies funded by the European Commission. Dr. van der Voort reported being involved in clinical trials of companies that market drugs for MS, and working with some that have development programs for future drugs for the disease. ■