

Understanding Neutralizing Antibodies

The clinical importance of neutralizing antibodies (NABs) as immunomodulatory therapies for multiple sclerosis (MS) remains controversial. Several studies presented at the ECTRIMS meeting attempted to shed more light on the nature and significance of NABs.

Understanding NAB Effects

The first study to assess the impact of NABs on Multiple Sclerosis Functional Composite (MSFC) scores found a negative effect among patients who received interferon- β (IFN- β) for at least 18 months and developed NABs. Dilaver Kaya, presenting on behalf of the Dokuz Eylül University Neuroimmunology Study Group, Izmir, Turkey, indicated that anti-IFN NABs (identified in 9 of 99 IFN- β -treated patients) were associated with significantly worse scores on the MSFC ($P=0.008$), as well as on the 9-Hole Peg Test and the Timed 25-Foot Walk Test (both tests $P\leq 0.01$). In contrast, NAB positivity did not seem to exert a negative influence on cognition, as measured by the Paced Auditory Serial Addition Test component of the MSFC and the Auditory Consonant Trial.

The development of NABs to recombinant IFN- β therapy appears to block the activity of endogenous IFN- β , reported Per Soelberg Sørensen, Rigshospitalet and Copenhagen University Copenhagen, Denmark. Research by his group showed that the expression of interleukin 10 (IL-10) was significantly lower in 36 MS patients with anti-IFN- β NABs than in 36 treatment-naïve patients and matched healthy controls. The expression of IL-10 correlated with the expression of *MX-1*, a gene used as a marker of IFN- β bioactivity in MS. On multivariate regression analysis, IL-10 was also independently associated

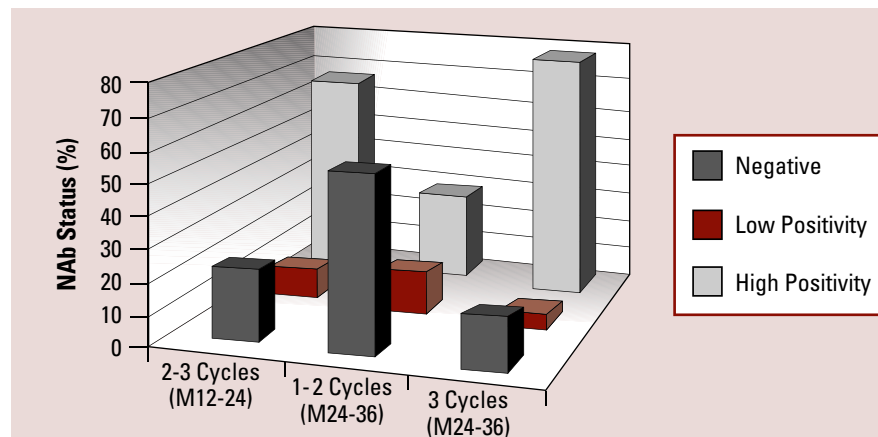


Figure. Positivity for NABs in MS patients treated with alemtuzumab.

with a lower number of active lesions on brain MRI. The investigators suggested that these observations reflect the presence of an endogenous immunoregulatory network controlled by IFN- β in MS. Endogenous IFN- β seems to exert a protective effect that is mimicked by recombinant IFN- β .

Dorothea Buck, Technische Universität, Munich, Germany, described the discovery of 2 new HLA alleles—1 associated with the development of anti-IFN- β antibodies (NABs or binding antibodies) and 1 associated with protection against such antibodies. Building on previously reported work, Dr. Buck and colleagues confirmed a significant link between the HLADRB1*1601 allele and antibody development ($P<0.001$). The HLADRB1*1104 allele conferred protection against anti-IFN- β antibodies.

NABs With MAB

Antibodies to alemtuzumab develop in most patients who receive this agent but do not seem to affect short-term efficacy or safety, according to Krzysztof Selmaj,

Medical University of Łódź, Łódź, Poland. On behalf of the CAMMS223 Study Group, Dr. Selmaj presented findings from 334 patients with early, active relapsing-remitting MS who were randomized to alemtuzumab (12 or 24 mg/d for 5 days at month 0, 3 days at month 12, and 3 days at month 24) or subcutaneous interferon β -1a (SC IFN β -1a; 44 μ g 3 times/wk). The third alemtuzumab dose was optional; 96% of patients assigned to this treatment received at least 2 cycles, and 21% received 3 cycles. The majority of patients who received ≥ 2 cycles of alemtuzumab demonstrated immune responses (Figure). Antibody concentrations peaked approximately 1 month after each treatment cycle and declined thereafter, until the patient was again exposed to the drug. Notably, during 3 years of follow-up and up to 3 annual treatment cycles, anti-alemtuzumab antibodies were not associated with changes in either efficacy (measured in terms of freedom from relapse, sustained accumulation of disability, or both) or the incidence of adverse events. ■

Measuring Quality of Life in MS Patients

Issues related to quality of life (QoL) in patients with multiple sclerosis (MS) have been attracting increased interest, as reflected by a wide range of presentations on this topic at ECTRIMS.

Studies Suggest Improved QoL With DMTs

Long-term treatment with disease-modifying therapies (DMTs) improved mental, but not physical, domains of health-related QoL in a study of 129 women with relapsing-remitting MS (RRMS). Sharon A. Warren, University of Alberta, Edmonton, Alberta, Canada, indicated that scores on subscales of the Short Form-36 (SF-36) Health Status Survey showed significant improvements in all mental domains (vitality, social functioning, role limitations due to emotional health, and mental health) after 1 and 3 years of treatment with DMTs. Conversely, scores reflecting bodily pain and role limitations due to physical function increased significantly at year 1, and measures of physical functioning and general health decreased significantly at year 3. Summary scores on the SF-36 mirrored these findings. The investigators pointed out that psychosocial well-being has been reported to be the most salient aspect of health-related QoL among women with RRMS, suggesting that DMTs may confer benefits—including improve-

ments in mental QoL—even if physical well-being does not improve.

A study of 224 patients with RRMS found that QoL remained stable or increased during therapy with glatiramer acetate (Copaxone®) for a mean of 22 months. Thibault Moreau, Centre Hospitalier Universitaire de Dijon, Dijon, France, explained that this work also provided initial validation of the Subjective Quality of Life Perception (SQLP) Questionnaire. Over a 10-month treatment period, results on the somatic and “diverse” domains of the SQLP improved significantly ($P=0.002$ and $P=0.012$, respectively), as did the social dimension of the Fatigue Impact Scale and the anxiety dimension of the Hospital Anxiety and Depression Scale. In addition, the SQLP domains proved sensitive to variations in EDSS scores.

Results from 56 patients with RRMS showed greater improvements in QoL among those who received natalizumab (Tysabri®) for ≥ 12 months than among those who received infusions of the drug for only 6 months, reported L. Thormählen, Heinrich-Heine University, Düsseldorf, Germany. Longer-term therapy produced superior results on all subscales of the SF-36. Scores on the EDSS improved significantly (by 17.4%) after 6 months of natalizumab treatment, but

they improved even more (by 18.5%) after 12 months of treatment.

Pain Associated With QoL, Clinical Disability

Results from 225 MS patients in the 12-month Real-World Betaseron Outcomes Study (ROBUST) revealed that self-perceived pain interfering with work correlates with reduced health-related QoL, according to data presented by Douglas Jeffery, Wake Forest University School of Medicine, North Carolina, and coauthors. Increases in ratings of the impact of pain were associated with significant decreases in SF 12-Item Health Survey Physical Component Scores (PCS-12; $P<0.0001$) and Mental Component Scores (MCS-12; $P=0.0032$). The degree of self-perceived depression in the ROBUST subjects was associated with a significant reduction in the MCS-12 ($P<0.001$) but not in the PCS-12. Changes from baseline in scores on the Expanded Disability Status Scale (EDSS) correlated significantly with the degree of perceived pain ($P<0.0001$) but not with the degree of perceived depression. **[Editor's Note: Dr. Stephen Kirzinger, an editor of this issue of Neura Special Report and an editor of Neura, served as a coinvestigator of this study.]**

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Impact of Social Support on MS QoL

Italian investigators have found that social support increases QoL in patients with MS but has no effect on the presence or severity of depression. Enrico Montanari, Ospedale di Fidenza, Parma, Italy, and his group evaluated 53

patients with RRMS who had been diagnosed at least 2 years previously and were clinically stable. The patients were divided into 3 clusters according to whether their social support was considered good (49%), problematic (reflecting a poorer degree of perceived support; 19%), or low (32%). Greater social support correlated with improved

scores on the Multiple Sclerosis Quality of Life instrument. Overall, depression was mild in 18.4% of patients, moderate in 8.2%, moderate to “harsh” in 6.1%, and “harsh” in 2%. Depression was not seen in 65.3% of the patients. Median scores on the Beck Depression Inventory did not vary significantly by level of social support. ■

Data Suggest Neuroprotective Effects

Experimental and clinical studies are adding to the body of data on potential neuroprotective effects of a variety of therapies in multiple sclerosis (MS).

A study of chronic relapsing experimental autoimmune encephalomyelitis (EAE) in rats has found that suppression of reactive gliosis may contribute to the therapeutic effects of BG00012, an investigational oral formulation of dimethyl fumarate, observed in MS clinical trials. Research described by Pradeep Bista, Biogen Idec, Inc., Cambridge, Massachusetts, showed that BG00012 reduced the activation of microglia and astrocytes, which play pivotal roles in neuroinflammation. Such activation occurs prior to the onset of symptoms and axonal damage in rodent models of MS. The agent has also been shown to prevent demyelination and neuronal loss. Taken together, these observations suggest dual anti-inflammatory and neuroprotective mechanisms of action. BG00012 significantly reduced gadolinium-enhancing lesions and reduced T1 hypointense black holes in phase II clinical trials. Phase III trials of BG00012 in relapsing-remitting MS (RRMS) are currently under way.

Other work has suggested that interferon (IFN) β -1b (Betaseron[®]) likewise has dual mechanisms of action, involving regulation of both anti-inflammatory and neuroprotective events. Ed Croze, Bayer HealthCare Pharmaceuticals, Richmond, California, presented research demonstrating that IFN β -1b induces the expression of metallothioneins (MTs), a family of enzymatic binding proteins with anti-inflammatory and neuroprotective properties. Upregulation of certain MT family members occurred after single doses or 2 months of treatment with IFN β -1b in patients with RRMS. Induction of MT gene

expression by IFN β -1b was confirmed and validated in further analyses of peripheral blood mononuclear cells from RRMS patients as well as from healthy subjects. Furthermore, MT induction was demonstrated in human fetal brain cells and astrocytes, suggesting a role for IFN β -1b in regulating MT expression in the central nervous system.

A case-control study using diffusion-weighted imaging (DWI) found significant recovery from microscopic tissue damage in patients with RRMS who received glatiramer acetate (Copaxone[®]) for a mean of 2.3 years. According to Robert Zivadinov, University of Buffalo, Buffalo, New York, data from 19 patients showed that the change in DWI mean parenchymal diffusivity from baseline was -7.1% ($P=0.007$) at 1 year and -10.1% ($P=0.028$) at 2 years. The degree of improvement was significantly greater in the patients than in matched normal controls at both 1 and 2 years ($P=0.03$ and $P<0.01$, respectively). The patients did not develop marked global or regional atrophy over the course of follow-up. The percent brain volume change was -0.8% , and gray matter volume changed by -1.2% ; neither of which was significant. The investigators concluded that the recovery from DWI entropy during therapy with glatiramer acetate was predictive of neural repair at 2 years.

A study of 9 RRMS patients produced evidence that glatiramer acetate prevents neurodegeneration, reported J. Jaworski, Linköping University, Linköping, Sweden. The patients were evaluated via proton magnetic resonance spectroscopy (¹H-MRS) at baseline before starting treatment. Follow-up ¹H-MRS was then performed at 1 year in 7 patients, at 2 years in 1 patient, and after 4 years in 1 patient. Relative concentrations of brain

metabolites with respect to creatine exhibited stability over time, with no significant differences in the successive measurements of *N*-acetylaspartate (NAA), myo-inositol (myo-Ins), choline, tissue noradrenaline, glutamate, or combined glutamate/glutamine. Dr. Jaworski pointed out that the natural history of MS is characterized by continuous loss of NAA and by constantly increasing gliosis (as reflected by myo-Ins) on ¹H-MRS, indicating progressive neurodegeneration. He stated that the prevention of such pathologic changes by glatiramer acetate could well indicate that this therapy can prevent or even reverse axonal and neuronal degeneration in MS.

The results of a phase II trial have suggested that oral temsirolimus may have a neuroprotective effect in addition to anti-inflammatory action in MS, reported Frederik Barkhof, VU University Medical Center, Amsterdam, The Netherlands. This analysis was based on data from 297 MS patients randomized to receive temsirolimus (2, 4, or 8 mg/d) or placebo for 9 months. Brain volume was evaluated using the (SIENA) method for T1-weighted images and brain parenchymal fraction (BPF) for PD/T2-weighted images. Temsirolimus significantly reduced the rate of brain atrophy as measured by both methods. Compared to placebo, temsirolimus 8 mg produced complete stabilization of even minor increases in brain volume: $+0.14\%$ (SE=0.13%) for SIENA and $+0.02\%$ (SE=0.07%) for BPF ($P=0.0063$ and $P=0.0015$, respectively). Dose-dependent effects on the rate of brain volume decrease were apparent with both assessment methods, although the effects of the lower doses (2 and 4 mg/d) remained significant vs placebo ($P=0.042$ and $P=0.0092$, respectively). ■

Immune Cell Effects of Oral Therapies

Several presentations at ECTRIMS explored interactions between oral therapies being developed to treat multiple sclerosis (MS) and immune cells.

According to M. Gurevich, Sheba Medical Center, Tel Hashomer, Israel, in vitro experiments have demonstrated that laquinimod, an oral investigational agent, induces a variety of immunomodulatory effects in the peripheral blood mononuclear cells of patients with relapsing-remitting MS (RRMS). His study found that these effects include activation of CD4+-related Th2 anti-inflammatory pathways, suppression of CD8+ T-cell proliferation, activation of negative regulators of inflammation in CD14+ macrophages, suppression of adhesion in CD19+ B cells, and suppression of natural killer (NK) cell-specific cytotoxic activity.

Other work has revealed that laquinimod increases levels of neurotrophic factors in vivo, potentially contributing to neuroprotective effects in patients with MS. This analysis, described by Jan Thöne, Ruhr-Universität Bochum, Bochum, Germany, involved 596 serum samples from patients with RRMS who received laquinimod 0.6 mg or placebo in a clinical trial. At 3 months, serum levels

of brain-derived neurotrophic factor increased by as much as 11-fold in the laquinimod group, reaching a mean of $16,088 \pm 760$ pg/mL. This increase was significant compared to baseline ($14,436 \pm 778$ pg/mL; $P < 0.05$) and to levels in the placebo group at 3 months ($12,882 \pm 625$ pg/mL; $P < 0.05$).

An analysis from the phase III CLARITY trial has shown that the investigational oral agent cladribine, a synthetic deoxyadenosine analogue, produces rapid and sustained decreases in peripheral lymphocyte subtypes that have been implicated in the pathogenesis of MS, noted Peter Rieckmann, University of British Columbia, Vancouver, British Columbia, Canada. Lymphocyte surface marker analysis in 300 patients treated with cladribine 3.5 or 5.25 mg/kg or placebo suggested that the drug has direct effects on T-cell function, humoral B-cell activity, and antigen-presenting cell activity. The observation that hematologic cell types have differential sensitivities to cladribine might reflect differences in intracellular levels of enzymes involved in metabolism of the drug, Dr. Rieckmann stated. Neutrophils and other hematologic components were relatively preserved during cladribine treatment, which could partially explain the lack of oppor-

tunistic and disseminated infections with cladribine treatment, as well as the drug's favorable tolerability profile, in the CLARITY study.

Additional insights into the mechanisms of action of cladribine have been gained through cellular expression profiling of genes involved in its metabolic pathway, reported Catherine Salvat, Merck Serono SA, Geneva, Switzerland. Differential mRNA expression of enzymes involved in cladribine metabolism was observed across various cell types, possibly explaining the targeted effects of the drug on lymphocyte subtypes that have been observed in MS patients. The study also suggested that differing sensitivities of cells to cladribine may be due to differences in the ratio of deoxycytidine kinase (DCK) to 5' nucleotidases (NTases) among immune cell subtypes as well as in the specific mRNA expression profiles of various members of the 5' NTase family. Other profiling studies have shown that DCK and the ratio of DCK to 5' NTases are high in T cells but very low in numerous nonhematologic cell types. Dr. Salvat noted that a lack of sensitivity to cladribine in nonhematologic cells would be expected to be favorable in terms of the adverse event profile of the drug. ■

B Cells: Disease and Treatment Effects

Effects of multiple sclerosis (MS) and its treatment on B-cell function were described in 2 studies presented at the ECTRIMS meeting.

BAFF Levels Decreased in CSF of MS Patients

In contrast to expected findings, investigators found a decreased level of B-cell activating factor (BAFF) in the cerebrospinal fluid (CSF) of patients with newly diagnosed MS, reported K. Faltermeier, Justus Liebig Universität, Giessen, Germany. The researchers anticipated that BAFF levels would be increased in such individuals, as the lig-

and has recently been shown to play a key role in regulating B-cell development and survival and has been shown to be involved in the pathophysiology of various autoimmune diseases. However, the analysis revealed that the mean CSF level of BAFF was 0.14 ± 0.11 ng/mL among 41 MS patients, compared to 0.18 ± 0.13 ng/mL among healthy controls ($P < 0.05$). No significant difference in serum levels of BAFF was evident between the groups. To explore the possibility that CSF BAFF is dependent on blood-brain barrier function, the investigators calculated the ratio of CSF albumin to serum albumin (Q Alb) and correlated the values with CSF BAFF in a

linear regression analysis. The Q Alb did not correlate significantly with BAFF levels in the CSF. The researchers concluded that the pathophysiologic basis of a decrease in CSF BAFF in MS requires further study.

Memory and Naïve B-Cells in RRMS

A study exploring the effects of MS and its treatment on memory and naïve B cells has suggested that such cell subsets might be important in both the pathogenesis and the treatment of MS. Masaaki Niino, Hokkaido University

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Graduate School of Medicine, Sapporo, Japan, described an analysis of blood samples from 31 patients in the remitting stage of relapsing-remitting MS (RRMS), of whom 15 were treated with interferon (IFN) β -1b and 16 were untreated. For 11 of the 16 untreated patients, blood samples were also obtained in the relapsing stage. Percentages of CD86+ and CCR5+ cells in the naïve-B-cell subset were significantly higher in untreated patients than in treated patients or in a group of 22 healthy controls.

More data from this study have been published in Niino et al. *Neurosci Lett.* 2009;464:74-78.

Among the MS patients, the percentages of CD86+ cells and CCR5+ cells in the naïve-B-cell subset and the percentage of CD5+ cells in the memory-B-cell subset were significantly greater during the remitting stage than during the relapsing stage. The finding that CCR5 positivity in naïve B cells decreased in response to IFN β -1b was consistent with previously reported studies of patients with RRMS. The observed increase in CCR5 positivity during the remitting

stage was of particular interest in light of recent work demonstrating that macrophages and microglia within early remyelinating lesions primarily express

CCR5. Dr. Niino suggested that the increase documented in the study suggests a potential role of CCR5+ B cells in initiating remyelination. ■

Long-Term Outcomes of Progressive MS Subtypes

New retrospective chart reviews have revealed that long-term outcomes are poorer in secondary-progressive multiple sclerosis (SPMS) than in primary-progressive MS (PPMS), according to Nilufer Kale, Mayo Clinic, Rochester, Minnesota. These findings stand in contrast to those of most natural history studies, which have found that PPMS is associated with the worst outcomes from the time of disease onset.

To explore these issues in more depth, Dr. Kale's group analyzed data from approximately 800 patients with progressive forms of MS. Those with SPMS had a more favorable early disease course but eventually experienced worse outcomes than patients with other progressive subtypes. From the time of disease onset, patients with PPMS reached motor disability milestones (scores of 3 or 6 on the Expanded Disability Status Scale [EDSS]) significantly faster than did those with SPMS, clinically isolated syndrome (CIS) plus progression, or other progressive subtypes ($P < 0.001$). From the onset of progression, however, patients with SPMS reached EDSS scores of 6 or 8 significantly faster compared with the other groups ($P < 0.001$).

An additional analysis, focusing on determinants of long-term disability, found that clinical and demographic factors determining long-term outcome were relatively similar among patients with various subtypes of progressive MS once progression had been established. One notable observation was that the number of early attacks and poor recovery from such attacks predicted worse long-term outcomes in patients with SPMS. ■

Treatment Reduces MS Spasticity

The results of 2 recent studies suggest that nabiximols (Sativex®), an endocannabinoid system modulator, significantly reduces spasticity in patients with multiple sclerosis (MS) and maintains its efficacy over the long term.

As described by Z. Ambler, Neurologicka Klinika FN Plzeň, Plzeň, Czech Republic, the first study began with a single-blind, 4-week treatment period aimed at identifying patients capable of responding to nabiximols. Response was defined as a decrease of $\geq 20\%$ in spasticity score on a mean numerical rating scale (NRS). Of 572 patients evaluated, 272 (48%) were deemed responders and 241 entered a subsequent double-blind phase, in which they were randomized to receive nabiximols or placebo for

12 weeks. A significantly greater reduction in spasticity from baseline was achieved with nabiximols than with placebo ($P = 0.0002$). Analyses of second-

ary endpoints revealed additional benefits of nabiximols, including a significantly lower frequency of spasms over

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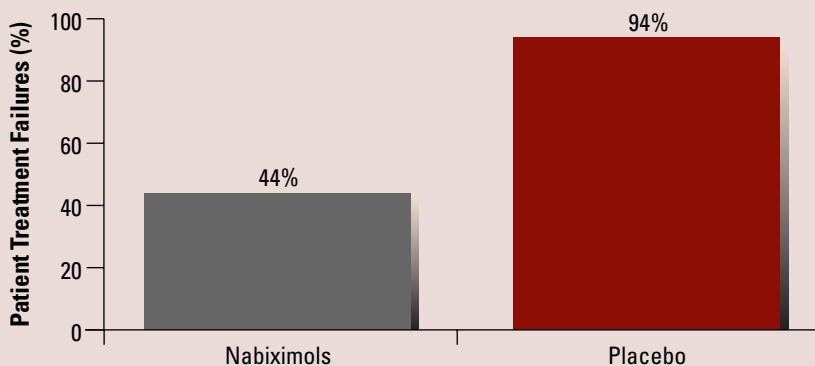


Figure. Proportion of treatment failures in patients taking nabiximols vs placebo.

Treating Spasticity

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the course of the study ($P=0.0046$) and a higher proportion of patients with $\geq 30\%$ improvement from baseline on the NSR ($P=0.0003$). Assessments of adverse events (AEs) showed nabiximols to be well tolerated. The most common AEs included headache, somnolence, dry mouth, and vertigo.

In the second study, patients receiving nabiximols on an investigational basis entered a 7-day baseline period during which they continued at their current doses. As described by William Notcott, James Paget Hospital, Great

Yarmouth, England, and colleagues, treatment was then stopped, and 36 patients were randomized to receive either nabiximols (at their previous stable doses) or placebo for 4 weeks. By the end of this withdrawal phase, the proportion of treatment failures was greater in the placebo group, than in the nabiximols group (Figure). The hazard ratio for treatment failure with nabiximols vs placebo was 0.335 (90% CI: 0.162 to 0.691; $P=0.013$). Analyses of secondary endpoints showed that nabiximols was significantly superior to placebo with respect to scores on the

Subject Global Impression of Change and Clinical Global Impression of Change (functional ability) scales ($P=0.017$ and $P=0.001$, respectively). Treatment-related AEs occurred in 50% of the nabiximols group and 56% of the placebo group during the 4-week, randomized phase; of these patients, 11% and 50% in each group, respectively, stopped treatment due to an adverse event. No evidence of a withdrawal syndrome was seen in the patients who had switched from nabiximols to placebo, even though they had received the medication for prolonged periods of time. ■

Posttreatment Activity and JC Virus

Data on the return of disease activity after treatment discontinuation and the detection of JC virus (JCV) were reported in several presentations on natalizumab (Tysabri®).

Increase in ARR

Paul W. O'Connor, St. Michael's Hospital, Toronto, Ontario, Canada, described findings from 946 patients who stopped treatment with natalizumab when the drug was temporarily removed from the market and from clinical trials in 2005. All these individuals had been randomized to natalizumab in "feeder studies" (AFFIRM, SENTINEL, or GLANCE) and had continued to receive the drug in a safety extension study. The patients returned for safety evaluations at the time they stopped natalizumab and then every 3 months for at least 6 months. After cessation of treatment, the monthly annualized relapse rate (ARR) initially remained stable but soon began to increase, reaching 0.58 (95% CI: 0.41, 0.78) at 4 months. The ARR was 0.49 (95% CI: 0.43, 0.56) over the entire observation period of 8 months. In contrast, the ARR during natalizumab therapy in the feeder studies was 0.28 (95% CI: 0.25, 0.32). Patients who had highly active disease at the time of enrollment in the feeder studies exhibited the greatest increase in ARR after cessation of natalizumab, reaching a rate of 1.56 (95% CI: 0.96, 2.38) at month 4. Of the 946 patients in the overall analysis,

402 received disease-modifying therapy (DMT) with interferon (IFN) β -1a or glatiramer acetate after stopping natalizumab. Treatment with either DMT did not seem to delay the return of disease activity, as the ARR increased to 0.63 (95% CI: 0.38, 0.99) in the DMT group and to 0.54 (95% CI: 0.34, 0.81) in the no-DMT group by month 4. However, the investigators pointed out that no firm conclusions could be reached regarding the effects of DMTs because of the small sample size and the uncontrolled nature of the treatment decisions. Despite the increases in ARRs observed after cessation of natalizumab, disease activity did not rebound in excess of pretreatment levels.

JCV Detection

Richard A. Rudick, Cleveland Clinic Foundation, Cleveland, Ohio, reported that natalizumab treatment was not found to increase the prevalence of JCV viremia based on analyses of a large number of biological samples from patients in the STRATA study and from a safety evaluation study. Of nearly 2,400 patients from both studies, JCV viremia was found in $<1\%$. Additionally, JCV DNA was not detected in 4,066 peripheral blood mononuclear cell (PBMC) samples. Over 48 weeks, JCV was detected in 113 of 446 (25%) urine samples. Dr. Rudick noted that the prevalence of JCV viremia was consistent with

reported rates in healthy individuals and that, to date, no patient with detectable JCV in plasma who continued natalizumab therapy has developed PML.

Results of another study assessing the effect of natalizumab treatment on the active replication of JCV in patients with relapsing-remitting multiple sclerosis (RRMS) were presented by Maria Inmaculada Dominguez-Mozo, Hospital Clínico San Carlos, Madrid, Spain. Analyses of 597 PBMC, serum, and urine samples from 41 patients currently being treated with natalizumab (range 1–15 months) revealed that 75.6% of the patients had JCV DNA in their urine, but JCV DNA had not been detected in the serum or blood of any patient.

In a smaller study, however, JCV was detected in both the blood and urine of 19 patients receiving natalizumab. During an oral session atECTRIMS, Igor Koralnik, Harvard Medical School, Boston, Massachusetts, presented data from a study published by his group (*NEJM*. 2009;361:1067-1074). After 12 months of treatment, the prevalence of JCV in urine increased to 63% from the baseline value of 19% ($P=0.02$). In 3 of 15 (20%) plasma samples and 9 of 15 (60%) PBMC samples ($P=0.02$), JCV was detected. The presence of the virus in blood was detected after 18 months of treatment, which is a longer duration than that of other studies. None of the patients in this study developed PML. ■

Prevalence of CAM Use in the US

The use of complementary and alternative medicine (CAM) is prevalent among patients with multiple sclerosis (MS) but is primarily confined to taking vitamin supplements, reported Kurt Johnson, University of Washington, Seattle, Washington.

The analysis described by Dr. Johnson was based on data from the fifth survey within an ongoing longitudinal study of MS outcomes. Among 458 patients in a community-based sample, 81% indicated that they currently use some type of CAM. The majority of the CAMs currently used were vitamin supplements (Figure). Fewer than 13% of respondents indicated that they currently use massage, yoga, special diets, herbal supplements, homeopathy, acupuncture, hypnosis, or chiropractic treatment.

According to present expert consensus, vitamin D supplements are to be considered for all patients with MS, Dr. Johnson noted. The fact that 42% of survey partici-

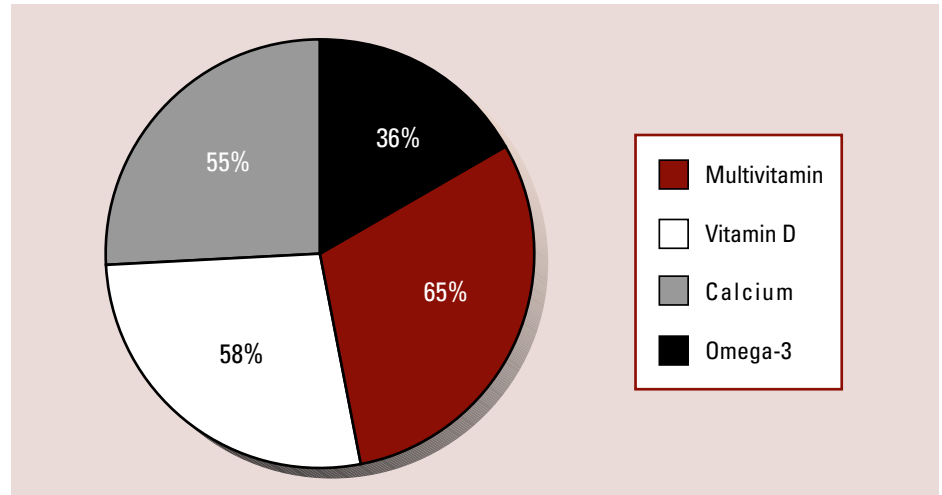


Figure. Current use of vitamin supplements reported by MS patients.

pants did not report current use of vitamin D suggests that many healthcare providers may not be communicating this information to their patients. Furthermore, as CAM has the potential to exacerbate con-

comitant conditions or interact with conventional medicines, it is imperative that healthcare providers address the pros and cons of all types of alternative therapies with their patients. ■

Dental Care Overlooked in MS Patients

Many patients with multiple sclerosis (MS) suffer from poor dental health, which can lead to infection and worsened immunologic status, according to Yára Dadalti Fragoso, UNIMES and MS Reference Center DRS IV, Santos, Brazil.

Dr. Fragoso described findings from 21 MS patients who underwent clinical and radiologic oral evaluations. Of this group, 15 individuals had visited a dentist at least once per year, whereas the other 6 saw a dentist on a less regular basis. The mean O'Leary index (a plaque indicator reflecting the risk of tooth loss) was 45.6% (range, 11.9% to 85.6%). A total of 16 patients (72.7%) had an O'Leary index >30%, signifying a risk of losing teeth. Compared to matched controls with no underlying disease, the MS patients had significantly higher rates of tooth loss ($P=0.035$), silent infection ($P<0.0001$), and temporomandibular dysfunction ($P=0.003$). So-called "parafunctional"

habits (such as nail biting and lip biting) were noted in twice as many MS patients as controls (54.5% vs 27.2%). No correlations were apparent between demographic or disease characteristics (including gender, age, disability, MS duration, current or previous immunomodulator therapy, and number of corticosteroid pulses) and the occur-

rence of tooth loss, infection, or temporomandibular dysfunction. Dr. Fragoso pointed out that a typical multidisciplinary team caring for MS patients does not include a dentist, despite evidence that suggests infections exacerbate both clinical relapses and measures of disease.

The patients in this study had not been suspected to have silent infections until specialized dentists conducted full clinical and radiologic evaluations. Another consideration is that pain associated with temporomandibular dysfunction (which can arise from tooth loss or parafunctional habits) is known to lead to distress, anxiety, and depression—factors that can further undermine quality of life in patients with MS. Based on these observations as well as the results of their study, Dr. Fragoso and colleagues recommended that a specifically trained dental surgeon be part of the team caring for patients with MS. ■

The following articles present more data on the suggested link between infection and MS relapse risk: Correale J, Farez M. *Journal of Neuroimmunology*. 2007;190:177-189 and Correale J, Fiol M, Gilmore W. *Neurology*. 2006;67:652-659.

**SPECIAL
REPORT**

Presents

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Highlights From the 25th Congress of the European
Committee For Treatment and Research in Multiple Sclerosis

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