Effect of Teriflunomide on Cells From Patients With Human T-cell Lymphotropic Virus Type 1–Associated Neurologic Disease

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Abstract

Objective
To test the hypothesis that teriflunomide can reduce ex vivo spontaneous proliferation of peripheral blood mononuclear cells (PBMCs) from patients with human T-cell lymphotropic virus type 1 (HTLV-1)–associated myelopathy/tropical spastic paraparesis (HAM/TSP).

Methods
PBMCs from patients with HAM/TSP were cultured in the presence and absence of teriflunomide and assessed for cell viability, lymphocyte proliferation, activation markers, HTLV-1 tax and HTLV-1 hbz messenger ribonucleic acid (mRNA) expression, and HTLV-1 Tax protein expression.

Results
In culture, teriflunomide did not affect cell viability. A concentration-dependent reduction in spontaneous proliferation of PBMCs was observed with 25 μM (38.3% inhibition), 50 μM (65.8% inhibition), and 100 μM (90.7% inhibition) teriflunomide. The inhibitory effects of teriflunomide were detected in both CD8+ and CD4+ T-cell subsets, which are involved in the immune response to HTLV-1 infection and the pathogenesis of HAM/TSP. There was no significant change in HTLV-1 proviral load (PVL) or tax mRNA/Tax protein expression in these short-term cultures, but there was a significant reduction of HTLV-1 PVL due to inhibition of proliferation of CD4+ T cells obtained from a subset of patients with HAM/TSP.

Conclusions
These results suggest that teriflunomide inhibits abnormal T-cell proliferation associated with HTLV-1 infection and may have potential as a therapeutic option in patients with HAM/TSP.
Human T-cell lymphotropic virus 1 (HTLV-1) is a retrovirus causing persistent infection in humans; a small subset of infected individuals develops HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP). HAM/TSP is a chronic, progressive, neurologic disease characterized by progressive lower extremity weakness, spasticity, and bladder/bowel sphincter dysfunction. Currently, no therapy significantly modifies long-term disability associated with HAM/TSP. HTLV-1 proviral load (PVL) is significantly elevated in peripheral blood mononuclear cells (PBMCs) and CSF of patients with HAM/TSP compared with asymptomatic carriers. Chronically activated immune responses against HTLV-1 and infiltration of inflammatory cells into the CNS contribute to clinical disability and underlie the pathogenesis of HAM/TSP.

Teriflunomide is an oral immunomodulator approved to treat MS that inhibits de novo pyrimidine synthesis, which is crucial for rapid expansion of activated lymphocytes. Pyrimidine synthesis inhibition is a well-established strategy for treatment of autoimmune diseases such as MS and rheumatoid arthritis. Teriflunomide has been shown to inhibit proliferation and reduce the number of activated T and B cells. In addition, teriflunomide and its parent compound leflunomide have been shown to have antiviral activity against a broad range of viruses in vitro and in vivo in humans, suggesting they might attenuate abnormal immune activation in patients with inflammatory diseases associated with chronic viral infection.

In this study, we examined whether teriflunomide can reduce the spontaneous lymphoproliferative response in culture of PBMCs from patients with HAM/TSP ex vivo, which is the immunologic hallmark of individuals infected with HTLV-1.

**Methods**

**Subjects**

A total of 12 patients, defined as having HAM/TSP by World Health Organization criteria, an HTLV-1–uninfected healthy donor (HD) volunteer screened at the NIH Clinical Center were evaluated in this report. In the patients, the mean age was 56.6 years, and the mean disease duration was 11.8 years. Patients with HAM/TSP were not being treated with any immunosuppressive agents at the time of PBMC collection.

**Cell Viability**

PBMCs of HDs and patients with HAM/TSP were isolated by centrifugation using lymphocyte separation media and were cryopreserved in liquid nitrogen until use. PBMCs were suspended in complete Roswell Park Memorial Institute medium supplemented with 5% human serum type AB, 100 U/mL penicillin, 100 μg/mL streptomycin sulfate, and 2 mM l-glutamine and plated in 96-well round bottom microplates at 3 × 10^5 cells/well with defined concentrations of teriflunomide (0, 1.5, 6.25, 25, and 100 μM), chosen as a wider range of concentrations than published previously for testing cell viability. The cells were cultured at 37°C/5% CO₂, and the cell viabilities were examined at 0, 1, 3, and 5 days using a Muse cell analyzer (Millipore).

**Lymphoproliferation Assay**

Lymphoproliferation assay using [³H] thymidine was performed as described previously. PBMCs of HDs and patients with HAM/TSP were cultured in triplicate in 96-well round bottom microplates at 3 × 10^5 cells/well with defined concentrations of teriflunomide (0, 25, 50, and 100 μM), which are comparable to concentrations achieved in vivo in pharmacokinetic studies of teriflunomide in patients with MS. The cells were pulsed after 3–5 days of culture with 1 μCi [³H] thymidine. The average counts per minute from each of the wells were determined.

Lymphoproliferation assay using carboxyfluorescein succinimidyl ester (CFSE) (CellTrace CFSE cell proliferation kit; Invitrogen) was performed as described previously. PBMCs were labeled with CFSE, according to the manufacturer’s instruction, and plated at 3 × 10^5 cells/well in 96-well round bottom microplates with defined concentrations of teriflunomide (0, 25, 50, and 100 μM). After culture for 4 and 5 days, the cells were stained with antibodies against CD3, CD4, CD8, and CD25 (all from BD Biosciences). The data were acquired on an LSRII flow cytometer (BD Biosciences) and were analyzed using FlowJo 10.5 software (FlowJo LLC).

**HTLV-1 PVL**

HTLV-1 PVL was measured using droplet digital polymerase chain reaction (PCR) (Bio-Rad) as described previously. PBMCs of patients with HAM/TSP were cultured at 2 × 10^6 cells/well in 12-well plates with defined concentrations of teriflunomide (0, 25, 50, and 100 μM) and collected after culture for 1, 3, and 5 days. Deoxyribonucleic acid (DNA) was extracted from the PBMC using a DNAeasy Blood and Tissue kit (Qiagen) according to the manufacturer’s instructions. Primers and probes specific for HTLV-1 tax and human ribonuclease P protein subunit 30 were used. The duplex PCR amplification was performed in this sealed 96-well plate using a GeneAmp 9,700 thermocycler (Applied Biosystems). Following PCR amplification, the 96-well plate was transferred to a QX100 droplet reader.
For PVL calculation, QuantaSoft software version 1.3.2.0 (Bio-Rad) was used to quantify the copies/μL for each queried target per well. All samples were tested in duplicate (a total of no less than 20,000 droplets), unless specified otherwise, and PVL is reported as the average of the 2 measurements.

**HTLV-1 tax/hbz Messenger Ribonucleic Acid Expression**

PBMCs of patients with HAM/TSP were cultured at 2 × 10^6 cells/well in 12-well plates with defined concentrations of teriflunomide (0, 25, and 50 μM) and collected after 20 hours. RNA was extracted from fresh-frozen PBMCs or cultured PBMCs using the RNAeasy plus mini kit (Qiagen), and cDNA was synthesized from extracted RNA using a high-capacity cDNA reverse transcriptase kit (Applied Biosystems). Measurements of HTLV-1 tax and hbz messenger ribonucleic acid (mRNA) were performed using ddPCR (Bio-Rad). The following primers and probes specific for HTLV-1 tax and HTLV-1 hbz were used: tax F (ATCCCGTGAGACTCTCTCAA); tax R (CCAAACACGTAGACTGGGTATCC); tax probe (6FAM-CCCCGCCGATCCAAA-MGB); hbz F (AGAACGCGACTCAACCGG); hbz R (TGACACAGGCAAGCATCGA); and hbz probe (6FAM-ATGGCGGCCTCAGGGCT-MGB). Primers and probes specific for hypoxanthine phosphoribosyl transferase (HPRT) were used for normalization (Thermo Fisher Scientific). Normalized values of HTLV-1 tax mRNA and hbz mRNA expression were calculated using the following formula: 

\[
\text{HTLV-1 tax mRNA or hbz mRNA} = \left( \frac{\text{the relative quantity of HTLV-1 tax mRNA or hbz mRNA}}{\text{the relative quantity of HPRT mRNA}} \right) \times 100
\]

All samples were tested in duplicate, and HTLV-1 tax and hbz mRNA expressions are reported as the average of the 2 measurements.

**Flow Cytometry**

PBMCs of patients with HAM/TSP were cultured at 3 × 10^5 cells/well in 96-well round bottom microplates with defined concentrations of teriflunomide (0, 25, 50, and 100 μM). After 20 hours, the cells were stained with antibodies for CD3, CD4, CD8, and CD25 (all from BD Biosciences). After treatment with fixation/permeabilization solution (eBioscience), the cells were stained with antibody for Tax (Lt-4). The data were acquired on an LSRII flow cytometer (BD Biosciences) and were analyzed using FlowJo 10.5 software (FlowJo LLC).

**Statistics**

Repeated-measures 1-way ANOVA was used to compare spontaneous lymphoproliferation, CD25^+ cells in the CD3^+ and CD8^+ T-cell populations, HTLV-1 PVL, and HTLV-1 tax mRNA and hbz mRNA expressions at different concentrations of teriflunomide treatment. All statistical analysis was performed using Prism (GraphPad software).
Standard Protocol Approvals, Registrations, and Patient Consents

The study was reviewed and approved by the NINDS Institutional Review Board. All clinical samples used in this study were collected at NINDS under protocol #98-N-0047. Before study inclusion, written informed consent was obtained from subjects in accordance with the Declaration of Helsinki.

Data Availability

All the data used for the article will be provided on request.

Results

Teriflunomide Inhibited Spontaneous Lymphoproliferation of PBMCs From Patients With HAM/TSP

Cell viability of PBMCs of a HD cultured with teriflunomide was examined, compared with that in the culture without teriflunomide. Teriflunomide (0, 1.5, 6.25, and 25 μM) did not affect cell viability during the culture for 5 days (<3.6% difference; figure 1A). The cell viability was slightly lower at 8.2% and 13.7% at day 3 and day 5 for cultured PBMCs with 100 μM teriflunomide, respectively (figure 1A). To determine whether teriflunomide has an inhibitory effect on ex vivo spontaneous lymphoproliferation of patients with HAM/TSP, we examined lymphoproliferation in cultured PBMCs of patients with HAM/TSP compared with an HD with defined concentrations of teriflunomide. As shown in figure 1B, PBMCs of an HD did not spontaneously proliferate and therefore were not affected by the addition of teriflunomide in the culture (figure 1B; left graph). By contrast, spontaneous lymphoproliferation was detected in the PBMC culture of a patient with HAM/TSP (HAM 1) without any exogenous stimuli after day 3 (figure 1B; right graph). Incubation with defined (25, 50, and 100 μM) concentrations of teriflunomide inhibited spontaneous lymphoproliferation in lymphocytes from this patient with HAM/TSP in a concentration-dependent manner (figure 1B; right graph). Group analysis of 12 patients with HAM/TSP also showed a concentration-dependent suppression in spontaneous lymphoproliferation between day 3 and day 5 (figure 1C). Group analysis of the effect of teriflunomide in HAM/TSP PBMC at a single time point (day 5) demonstrated a significant suppression of spontaneous lymphoproliferation in a concentration-dependent manner (p < 0.0001; figure 1D). Compared with spontaneous lymphoproliferation without teriflunomide, the average percentage...
increase across all the patients with HAM/TSP was 38.3%, 65.8%, and 90.7% at 25, 50, and 100 μM teriflunomide, respectively (figure 1E). These results demonstrated that teriflunomide reduced ex vivo spontaneous lymphoproliferation in PBMCs of patients with HAM/TSP.

**Teriflunomide Inhibited Both CD8+ and CD4+ T-Cell Proliferation of Patients With HAM/TSP**

In patients with HAM/TSP, CD8+ T cells have been demonstrated to predominantly proliferate in ex vivo PBMC cultures. Given the inhibitory effect of teriflunomide on ex vivo spontaneous lymphoproliferation in patients with HAM/TSP, we asked whether spontaneous lymphoproliferation of either CD8+ and/or CD4+ T cell is inhibited by teriflunomide in PBMC culture of patients with HAM/TSP. Figure 2A shows representative dot plots of spontaneous CD8+ and CD4+ T-cell proliferation of a patient with HAM/TSP (HAM 1) in PBMC culture at day 5 with and without teriflunomide using CFSE. Both CD8+ and CD4+ T cells showed spontaneous proliferation, although, as expected, CD8+ T cells proliferated to a greater extent than CD4+ T cells (figure 2A). After culture with teriflunomide 50 μM, both CD8+ and CD4+ T cells showed a reduction in spontaneous lymphoproliferation (figure 2A). Group analysis of spontaneous CD8+ T-cell proliferation in 12 patients with HAM/TSP showed a significant and concentration-dependent suppression in culture with teriflunomide at day 5 (p = 0.0025; figure 2B). The average percent inhibition across all the patients with HAM/TSP was 54.3%, 64.1%, and 84.9% at 25, 50, and 100 μM teriflunomide, respectively (figure 2C), which was consistent with proliferation assay using [3H] thymidine (figure 1E). Although CD4+ T cells of patients with HAM/TSP showed less proliferation than CD8+ T cells, spontaneous CD4+ T-cell proliferation was also significantly suppressed with teriflunomide in a concentration-dependent manner (figure 2D). Compared with spontaneous lymphoproliferation without teriflunomide, the average percent inhibition across all the patients with HAM/TSP was 46.1%, 54.2%, and 73.2% at 25, 50, and 100 μM teriflunomide, respectively (figure 2E).

These results demonstrated that teriflunomide inhibited proliferation of both CD8+ and CD4+ T cells in ex vivo PBMC culture of patients with HAM/TSP.

**Teriflunomide Did Not Change an Activation Marker of Patients With HAM/TSP**

Patients with HAM/TSP have high levels of CD25 (a chain of the interleukin (IL)-2 receptor) in T cells, particularly in CD4+ T cells that contain high HTLV-1 PVL and increased expression of HTLV-1 tax mRNA. To determine whether teriflunomide has an effect on CD25 expression associated with HTLV-1 infection, we examined the frequency of CD25+ T cells in both CD4+ and CD8+ T cells in cultured PBMCs from patients with HAM/TSP with defined concentrations of teriflunomide. In CD4+ T cells, there was no effect of teriflunomide on the frequency of CD25+ cells from patients with HAM/TSP through 5-day cultures compared with cultures without teriflunomide (figure 3A). In the presence of CD4+ T cells, CD8+ T cells showed less CD25 expression before culture, but the frequency of CD25+ cells increased in CD8+ T cells of patients with HAM/TSP, consistent with an increase in spontaneous proliferation in this T-cell subset after culture (figure 3B). In the presence of teriflunomide, a reduced frequency of CD25+ cells in CD8+ T cells was observed at day 5, although this did not reach statistical significance (figure 3B). The average percent inhibition across all the patients with HAM/TSP was 30.9%, 26.0%, and 41.1% at 25, 50, and 100 μM teriflunomide, respectively (figure 3B). These results demonstrate that teriflunomide had minimal effect on the immune activation marker CD25 of patients with HAM/TSP during these short-term ex vivo PBMC cultures.

**Teriflunomide Did Not Change HTLV-1 mRNA Expression of Patients With HAM/TSP, But Inhibited Expansion of HTLV-1 Infection**

Because teriflunomide has been suggested to have potential broad-spectrum antiviral activity against several viruses such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV), we next examined the effect of teriflunomide on HTLV-1 PVL, HTLV-1 mRNA, and HTLV-1 Tax protein expression in ex vivo spontaneous lymphoproliferation in patients with HAM/TSP.
vivo PBMC culture of patients with HAM/TSP. HTLV-1 PVL in cultured PBMCs from 6 patients with HAM/TSP with defined concentrations of teriflunomide was examined. Group analysis showed that HTLV-1 PVL remained stable in PBMCs of a patient with HAM/TSP in the culture for 1 day with and without teriflunomide compared with HTLV-1 PVL before culture (figure 4A). Although HTLV-1 PVL gradually increased in PBMC culture without teriflunomide from day 3 to day 5, the increase of HTLV-1 PVL was inhibited with teriflunomide (figure 4A). After 5 days of culture, HTLV-1 PVL was reduced in PBMCs of patients with HAM/TSP in a concentration-dependent manner and approached statistical significance ($p = 0.0626$; figure 4B). Of interest, teriflunomide was able to inhibit HTLV-1 PVL in some patients with HAM/TSP with high PVL (figure 4B; HAM 1, 8, and 10). Compared with HTLV-1 PVL in PBMC culture without teriflunomide, the average percent inhibition across all the patients with HAM/TSP was 18.4%, 30.2%, and 40.9% at 25, 50, and 100 μM teriflunomide, respectively (figure 4C).

In HAM/TSP, there is a spontaneous increase of HTLV-1 tax mRNA and HTLV-1 Tax protein expression in PBMCs after ex vivo culture without exogenous stimulators, which has been shown to peak at 12–24 hours in culture, although the HTLV-1 PVL remains stable during this short period. To determine whether teriflunomide has an effect on HTLV-1 expression, we examined HTLV-1 tax and hbz mRNA expression in cultured PBMCs from patients with HAM/TSP with defined concentrations of teriflunomide. As shown in figure 4D, teriflunomide did not show any significant or concentration-dependent inhibition of HTLV-1 tax mRNA expression in 20-hour cultured HAM/TSP PBMC, except for the reduction of tax mRNA in 1 patient with HAM/TSP (figure 4D). Teriflunomide also did not show any significant or concentration-dependent inhibition of HTLV-1 hbz mRNA expression in 20-hour cultured HAM/TSP PBMC (figure 4E). In addition, Tax protein expression in CD4+ cells from cultured HAM/TSP PBMC was not significantly changed by treatment with teriflunomide (figure 4F).
These results demonstrated that although teriflunomide did not directly affect HTLV-1 infection and expression in ex vivo PBMCs of patients with HAM/TSP in short-term cultures, teriflunomide reduced HTLV-1 PVL in ex vivo PBMCs of patients with HAM/TSP at day 5 when spontaneous lymphoproliferation was significantly inhibition in the culture.

Discussion

Chronically activated immune responses including T-cell proliferation and cytokotic activity of CD8+ T cells have been demonstrated to contribute to clinical disability and underlie the pathogenesis of HAM/TSP.24 In our study, the dihydroorotate dehydrogenase (DHODH) inhibitor teriflunomide reduced ex vivo spontaneous lymphoproliferation in PBMCs, which is a well-established measure of ex vivo T-cell activation in HAM/TSP. Inhibition of DHODH has been shown in clinical and preclinical studies to inhibit the proliferation of a number of cell types, but its modulation has not been previously shown to inhibit spontaneous lymphoproliferation in patients with HAM/TSP.

After culture of PBMCs from patients with HAM/TSP, T cells proliferate without exogenous stimulation, which is an immunologic hallmark of HAM/TSP.14,15 Mechanistically, this spontaneous lymphoproliferation is associated with an increased HTLV-1 gene expression in PBMCs, which induce proliferation of HTLV-1–infected and/or activated T cells by the common γ chain family of cytokines such as IL-2 and IL-15 in culture.20,25,26 A number of drugs and monoclonal antibodies have been reported to suppress inflammation and activation of lymphocytes, evidenced by inhibitory effects on spontaneous lymphoproliferation and cytokine expression in ex vivo PBMC culture of patients with HAM/TSP.25,27,28 and have been used in clinical trials for patients with HAM/TSP.29,30,31 Proliferation of T cells in HAM/TSP may also be associated with the immunopathogenesis of this disease because antigen-specific CD8+ T cells have been shown to be elevated in peripheral blood, even higher in the CSF, of patients with HAM/TSP, and have been shown to be present in CNS lesions.32,33,34 Recently, teriflunomide has been reported to modulate oxidative phosphorylation and aerobic glycolysis in activated T cells via functional inhibition of complex III of the respiratory chain and preferentially reduce the proliferation of high-affinity T cells.6 It was therefore of interest to determine whether teriflunomide could also reduce the abnormal proliferation of HTLV-1–specific CD8+ T cells in patients with HAM/TSP. In our study, teriflunomide significantly inhibited spontaneous CD8+ T-cell proliferation in PBMC culture of patients with HAM/TSP but did not affect cell viability or expression of the T-cell activation marker CD25 in 5-day cultured PBMCs, consistent with a previous report.16 These results demonstrate that teriflunomide was able to inhibit abnormal proliferation of lymphocytes without killing these cells.

In addition to inhibition of CD8+ T cell proliferation, teriflunomide also inhibited the spontaneous proliferation of CD4+ T cells in PBMC cultures of patients with HAM/TSP. Both CD4+ and CD8+ T cells are involved in the immunologic regulation of HTLV-1 infection and in the inflammatory process associated with the pathogenesis of HAM/TSP. CD4+ T cells are the predominant reservoir of HTLV-1 and display a high expression of HTLV-1 viral products in patients with HAM/TSP.35,36 In addition, CD4+ T cells isolated from patients with HAM/TSP display a pattern of clonal expansion ex vivo in the absence of malignancy.26 HTLV-1 also infects CD8+ T cells, albeit at lower frequency than CD4+ T cells, but the percentage of proliferating CD8+ T cells has been reported to be 2–5-fold higher than that of CD4+ T cells in ex vivo PBMC culture of patients with HAM/TSP.20,35 In HAM/TSP, T-cell proliferation is highly regulated and is associated with the expression of HTLV-1 Tax.20,25,37 HTLV-1 has developed numerous mechanisms to induce T cell proliferation in the absence of appropriate signals, such as transactivation of IL-2/IL-2Ra by HTLV-1 Tax.37 An additional disruptive effect of HTLV-1 Tax results from its impact on the ability of the cell-cycle machinery to regulate DNA replication and cell division. It has been reported that the clonal expansion of HTLV-1–infected T cells relies on 2 distinct mechanisms: HTLV-1 infection preventing cell death in CD8+ T cells while inducing CD4+ T cells into the cell cycle.26 Teriflunomide inhibits the action of DHODH via cell cycle arrest at the G1/S phase checkpoint and entry into the G2/M phases without cell death, where HTLV-1 Tax promotes cell cycle progression.38,39 In HTLV-1–infected subjects, it has been reported that the median proliferation rate of CD4+ CD45RO+ and CD8+ CD45RO+ T cells was 2.5% and 3.6% per day, respectively, and that the rate of CD4+ CD45RO+ T cell proliferation was significantly higher in patients with HAM/TSP than in asymptomatic carriers.40 In patients with MS treated with teriflunomide, a mild but consistent lymphopenia was observed due to the antiproliferative effects of teriflunomide.6 Of interest, distinct effects of teriflunomide treatment on different T-cell subsets have been reported in patients with MS, with an absolute reduction in T helper 1 (Th1) cells, but not Th2 or Th17 cells.6 Because the increase of HTLV-1–infected CD4+ CCR4+ T cells with Th1 markers has been reported in patients with HAM/TSP,41 teriflunomide might be targeting Th1-type cells in these patients. Further studies will be required to understand how teriflunomide inhibits proliferation of both CD4+ and CD8+ T cells in patients with HAM/TSP.

Teriflunomide also inhibited HTLV-1 PVL in relatively short-term cultures of HAM/TSP PBMCs, although HTLV-1 expression was not affected by treatment with teriflunomide. Leflunomide/teriflunomide has been shown to have antiviral activity against a broad range of viruses, such as CMV, EBV, herpes simplex virus 1, and BK polyomavirus, in vitro and in vivo in humans.10-13 Leflunomide has been shown to interfere with virion assembly of CMV but not to inhibit DNA synthesis, suggesting that this drug may potentially be used for its antiviral properties against CMV infection.13 Leflunomide has been increasingly used to treat human CMV and BK virus infection in organ transplant patients with immunosuppression.14 Recently, teriflunomide has been also reported to inhibit proliferation of EBV-transformed B cells as well as lytic
Collectively, the results in this study demonstrated that ex vivo, teriflunomide reduced spontaneous lymphoproliferation of PBMCs, both in CD4+ and CD8+ T-cell subsets, from HAM/TSP patients. These results suggested that teriflunomide inhibited abnormal T-cell proliferation associated with HTLV-1 infection. In addition to the ex vivo efficacy of teriflunomide, a better understanding of its mechanism of action will allow for future clinical use of teriflunomide in treatment of HTLV-1–associated diseases.

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Disclosure
Y. Enose-Akahata, N. Ngouth, and J. Ohayon, the NIH, have no conflicts of interest to disclose. M. Mandel, former employee of Sanofi. J. Chavin, employee of Sanofi. T. J. Turner, employee of Sanofi. S. Jacobson, the NIH, has no conflicts of interest to disclose. Go to Neurology.org/NN for full disclosures.

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