ORIGINAL ARTICLE

B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis

Stephen L. Hauser, M.D., Emmanuelle Waubant, M.D., Ph.D.,
Douglas L. Arnold, M.D., Timothy Vollmer, M.D., Jack Antel, M.D.,
Robert J. Fox, M.D., Amit Bar-Or, M.D., Michael Panzara, M.D.,
Neena Sarkar, Ph.D., Sunil Agarwal, M.D., Annette Langer-Gould, M.D., Ph.D.,
and Craig H. Smith, M.D., for the HERMES Trial Group*

ABSTRACT

From the Department of Neurology, University of California at San Francisco, San Francisco (S.L.H., E.W.); Montreal Neurological Institute, McGill University (D.L.A., J.A., A.B.-O.), and NeuroRx Research (D.L.A.) — both in Montreal; Barrow Neurology Clinics, Phoenix, AZ (T.V.); Mellen Center for Multiple Sclerosis, Cleveland Clinic, Cleveland (R.J.F.); Biogen Idec, Cambridge, MA (M.P.); and Genentech, South San Francisco, CA (N.S., S.A., A.L.-G., C.H.S.). Address reprint requests to Dr. Hauser at the Department of Neurology, University of California at San Francisco, 505 Parnassus Ave., Box 0114, San Francisco, CA 94143-0114, or at hausers@neurology.ucsf.edu.

*Other investigators who participated in the Helping to Evaluate Rituxan in Relapsing–Remitting Multiple Sclerosis (HERMES) Trial Group are listed in the Appendix.

BACKGROUND

There is increasing evidence that B lymphocytes are involved in the pathogenesis of multiple sclerosis, and they may be a therapeutic target. Rituximab, a monoclonal antibody, selectively targets and depletes CD20+ B lymphocytes.

METHODS

In a phase 2, double-blind, 48-week trial involving 104 patients with relapsing–remitting multiple sclerosis, we assigned 69 patients to receive 1000 mg of intravenous rituximab and 35 patients to receive placebo on days 1 and 15. The primary end point was the total count of gadolinium-enhancing lesions detected on magnetic resonance imaging scans of the brain at weeks 12, 16, 20, and 24. Clinical outcomes included safety, the proportion of patients who had relapses, and the annualized rate of relapse.

RESULTS

As compared with patients who received placebo, patients who received rituximab had reduced counts of total gadolinium-enhancing lesions at weeks 12, 16, 20, and 24 (P<0.001) and of total new gadolinium-enhancing lesions over the same period (P<0.001); these results were sustained for 48 weeks (P<0.001). As compared with patients in the placebo group, the proportion of patients in the rituximab group with relapses was significantly reduced at week 24 (14.5% vs. 34.3%, P=0.02) and week 48 (20.3% vs. 40.0%, P=0.04). More patients in the rituximab group than in the placebo group had adverse events within 24 hours after the first infusion, most of which were mild-to-moderate events; after the second infusion, the numbers of events were similar in the two groups.

CONCLUSIONS

A single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks. This trial was not designed to assess long-term safety or to detect uncommon adverse events. The data provide evidence of B-cell involvement in the pathophysiology of relapsing–remitting multiple sclerosis. (ClinicalTrials.gov number, NCT00097188.)

EXHIBIT
IPR2018-01403
2226

MULTIPLE SCLEROSIS, THE PROTOTYPI-cal inflammatory demyelinating disease of the central nervous system, is second only to trauma as a cause of acquired neurologic disability in young adults.[1] Multiple sclerosis usually begins as a relapsing, episodic disorder (relapsing–remitting multiple sclerosis), evolving into a chronic neurodegenerative condition characterized by progressive neurologic disability.[2]

The traditional view of the pathophysiology of multiple sclerosis has held that inflammation is principally mediated by CD4+ type 1 helper T cells. Therapies (e.g., interferon beta and glatiramer acetate) developed on the basis of this theory decrease the relapse rate by approximately one third[3,4] but do not fully prevent the occurrence of exacerbations or accumulation of disabilities, and they are largely ineffective against purely progressive forms of multiple sclerosis.[5] The α_4 integrin inhibitor natalizumab, a monoclonal antibody that disrupts lymphocyte movement into the central nervous system, is effective in preventing relapses and also reduces the risk of sustained progression of disability in relapsing–remitting multiple sclerosis.[6] The prevention of focal inflammatory lesions early in the disease may delay the development of progressive multiple sclero-

sis[7]; this underscores the importance of developing more effective therapies for relapsing–remitting multiple sclerosis.

In contrast to earlier concepts of disease suggesting that pathogenic T cells are sufficient for full expression of multiple sclerosis, it is now evident that autoimmune B cells and humoral immune mechanisms also play key roles.[8] The existence of a humoral component in multiple sclerosis has been implicitly recognized for decades, evidenced by the inclusion of cerebrospinal fluid oligoclonal bands and increased intrathecal IgG synthesis in the diagnostic criteria for multiple sclerosis.[9-11] The deposition of antibody and activation of complement associated with vesicular disintegration of the myelin membrane are present in most lesions in multiple sclerosis,[12-14] and autoantibodies directed against diverse antigens can also be detected in the cerebrospinal fluid of many patients with multiple sclerosis.[15] Memory B cells, which cross the blood–brain barrier, are believed to undergo restimulation, antigen-driven affinity maturation, clonal expansion, and differentiation into antibody-secreting plasma cells within the highly supportive central nervous system environment.[16] Clonally expanded populations of memory B cells
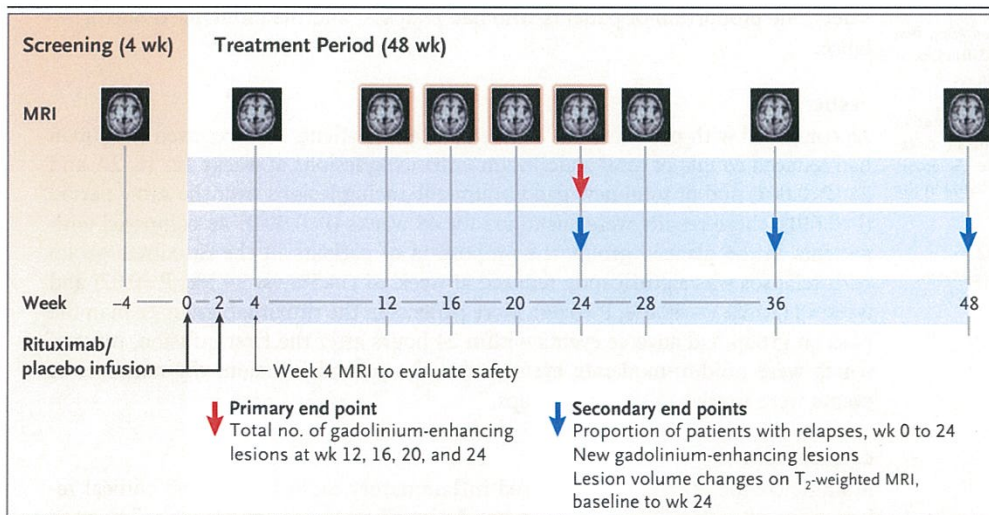

Figure 1. Study Design.

Patients were randomly assigned in a 2:1 ratio to receive rituximab or placebo. They were hierarchically stratified according to study site, status with respect to previous treatment with interferon beta or glatiramer acetate (either no treatment or discontinuation of medication >6 months previously vs. treatment within the previous 6 months), and baseline disease severity according to the Expanded Disability Status Scale (EDSS) score (≤2.5 vs. >2.5). The EDSS is an ordinal scale ranging from 0 (normal neurologic examination) to 10.0 (death) in 0.5-step intervals.

Table 1. Baseline Characteristics of the Patients.*

Variable	Placebo (N=35)	Rituximab (N=69)
Age — yr	41.5±8.5	39.6±8.7
Sex — no. (%)		
Female	29 (82.9)	52 (75.4)
Male	6 (17.1)	17 (24.6)
Disease duration — yr		
Since onset	9.6±7.1	9.6±6.4
Since diagnosis	6.9±6.2	6.2±5.2
Relapses in past year		
Relapses — no. of patients (%)		
0 relapses	2 (5.7)†	4 (5.8)†
1 relapse	27 (77.1)	52 (75.4)
2 relapses	5 (14.3)	8 (11.6)
3 relapses	0	4 (5.8)
≥4 relapses	1 (2.9)	1 (1.4)
Median (range)	1.0 (0–5)	1.0 (0–4)
EDSS score		
Score — no. of patients (%)		
0	1 (2.9)	2 (2.9)
1.0–1.5	8 (22.9)	9 (13.0)
2.0–2.5	10 (28.6)	24 (34.8)
3.0–3.5	7 (20.0)	20 (29.0)
4.0–4.5	7 (20.0)	11 (15.9)
5.0	2 (5.7)	3 (4.3)
Median (range)	2.5 (0–5)	2.5 (0–5)
Previous treatment with interferon beta or glatiramer acetate — no. of patients (%)		
None or discontinued >6 mo before study entry	21 (60.0)	44 (63.8)
Treatment within 6 mo before study entry	14 (40.0)	25 (36.2)
Any key therapy for MS in previous 2 yr — no. of patients (%)‡		
Glatiramer acetate	8 (22.9)	18 (26.1)
Interferon beta-1a	16 (45.7)	24 (34.8)
Interferon beta-1b	5 (14.3)	13 (18.8)
Methylprednisolone or methylprednisolone sodium succinate	8 (22.9)	19 (27.5)
Natalizumab	2 (5.7)	5 (7.2)
Any key therapy for MS — no. of patients (%)	27 (77.1)	54 (78.3)
Gadolinium-enhancing lesions		
No. of lesions — no. of patients (%)		
0 lesions§	30 (85.7)	44 (63.8)
1 lesion	2 (5.7)	7 (10.1)
2 lesions	2 (5.7)	4 (5.8)
3 lesions	0	2 (2.9)
≥4 lesions	1 (2.9)	11 (15.9)
Mean no. of lesions	0.3±0.8	2.1±5.6
Median no. of lesions (range)	0 (0–4)	0 (0–36)

Table 1. (Continued.)

Variable	Placebo (N = 35)	Rituximab (N = 69)
Volume of lesions detected on MRI — mm³		
On gadolinium-enhanced MRI		
Mean	29.2±127.5	211.6±702.2
Median	0	0
On T_2-weighted MRI		
Mean	5723.1±5514.8	6452.2±8022.2
Median	4032.0	2878.5
On T_1-weighted MRI		
Mean	717.6±1025.0	784.2±1206.4
Median	369.0	211.0

* Plus–minus values are means ±SD. EDSS denotes Expanded Disability Status Scale (range of scores, 0 to 10.0, with higher scores indicating more severe disease), MRI magnetic resonance imaging, and MS multiple sclerosis.
† These patients had relapses more than 1 year before study entry.
‡ Any key therapy for multiple sclerosis was defined as natalizumab, interferon beta, interferon beta-1a, interferon beta-1b, glatiramer acetate, azathioprine, immune globulin, methylprednisolone, methylprednisolone sodium succinate, or more than 20 mg of prednisone.
§ The proportion of patients without gadolinium-enhancing lesions was greater in the placebo group than in the rituximab group (85.7% vs. 63.8%, P=0.02); P values were calculated with the use of the chi-square test.

and plasma cells are found in lesions and cerebrospinal fluid from patients with multiple sclerosis,[17-21] and they can be detected even at the onset of clinical symptoms of the disease.[22] Abnormalities in B-cell cytokine responses have also been reported in patients with multiple sclerosis.[23]

Rituximab (Rituxan, Genentech and Biogen Idec) is a genetically engineered chimeric monoclonal antibody that depletes CD20+ B cells through a combination of cell-mediated and complement-dependent cytotoxic effects and the promotion of apoptosis.[24-26] B-cell depletion affects antibody production, cytokine networks, and B-cell–mediated antigen presentation and activation of T cells and macrophages.[27] On the basis of the effects of rituximab and the known immunopathology of multiple sclerosis, we performed a phase 2 trial of the agent in patients with relapsing–remitting multiple sclerosis.

METHODS

STUDY DESIGN AND RANDOMIZATION

The trial was a randomized, double-blind, placebo-controlled study conducted at 32 centers in the United States and Canada. The protocol was approved by the institutional review board and the ethics committee of each institution. Written informed consent was obtained from each patient or the patient's legal guardian. Patients were randomly assigned in a 2:1 ratio to receive rituximab or placebo (Fig. 1), and they were hierarchically stratified according to study site, status with respect to previous treatment with interferon beta or glatiramer acetate (either no treatment or discontinuation of medication ≥6 months previously vs. treatment within the previous 6 months), and baseline disease severity according to the Expanded Disability Status Scale (EDSS) score (≤2.5 vs. >2.5). The EDSS is an ordinal scale ranging from 0 (normal neurologic examination) to 10.0 (death) in 0.5-step intervals.[28] Patients received 1000-mg intravenous infusions of rituximab or placebo on study days 1 and 15 (Fig. 1).

The study was designed jointly by Genentech and the investigators. Data were collected by the investigators and held and analyzed by Genentech. All members of the publication committee had full access to the data. All the authors vouch for the veracity and completeness of the data and data analysis.

PATIENTS

Enrollment was limited to patients 18 to 55 years of age with a diagnosis of relapsing–remitting multiple sclerosis,[29] at least one relapse during

the preceding year, and an entry score of 0 to 5.0 on the EDSS. Exclusion criteria included disease categorized as secondary progressive, primary progressive, or progressive relapsing disease; relapse within 30 days; cyclophosphamide or mitoxantrone treatment within 12 months; systemic corticosteroid therapy within 30 days; treatment with interferon beta, glatiramer acetate, natalizumab, plasmapheresis, or intravenous immune globulin within 60 days; or non–lymphocyte-depleting immunosuppressive therapies within 90 days.

STUDY PROCEDURES AND END POINTS

To prevent potential breaks in blinding because of observed efficacy, adverse events, or changes in laboratory values, each site had both a treating investigator and an examining investigator. The treating investigator was the safety assessor and made all treatment decisions based on the patient's clinical response and laboratory findings. The examining investigator was the efficacy assessor, who administered the EDSS and Multiple Sclerosis Functional Composite Scale with access only to those data. Staff members from a central magnetic resonance imaging (MRI) reading center (NeuroRx, Montreal) who were unaware of the data evaluated all scans. Each site was instructed not to obtain MRI scans within 30 days after the last dose of corticosteroids prescribed for relapse, except for safety reasons.

At regularly scheduled visits over a period of 48 weeks, neurologic and physical examinations, MRI, and routine laboratory tests were performed and adverse events were recorded. After week 48, patients who remained peripherally B-cell–depleted continued in safety follow-up until their B-cell counts returned to the lower limit of the normal range or the baseline value, whichever was lower. Brain MRI scans with and without the administration of gadolinium were obtained at baseline and at weeks 4, 12, 16, 20, 24, 28, 36, and 48. Patients were evaluated for relapses at unscheduled visits if a clinically significant change in their condition occurred. Relapse was defined as new or recurrent neurologic symptoms that were consistent with multiple sclerosis, lasted for at least 48 hours, and were preceded by a relatively stable or improving neurologic state for at least 30 days. The treating investigator could treat relapses with systemic corticosteroids. In addition to routine laboratory tests, levels of CD19+ B cells,

immunoglobulins (IgG, IgA, and IgM), and human antichimeric antibodies were measured. Because rituximab interferes with flow-cytometric analysis of CD20, CD19, which has a similar expression profile, was used as a surrogate marker. The Common Toxicity Criteria, version 3.0,[30] were used to grade adverse events.

On days 1 and 15, acetaminophen (at a dose of 1 g) and diphenhydramine hydrochloride (at a dose of 50 mg) were administered orally 30 to 60 minutes before each infusion. Infusion-related reactions were to be treated with acetaminophen (paracetamol) plus intramuscular or slow intravenous administration of an antihistamine (diphenhydramine hydrochloride), a bronchodilator, or both, if indicated. If a severe infusion-related reaction occurred, the infusion was to be immediately interrupted, and symptomatic treatment initiated.

The primary efficacy end point was the sum of the number of gadolinium-enhancing lesions on serial T_1-weighted MRI brain scans at weeks 12, 16, 20, and 24. Thus, lesions that persisted for more than 4 weeks were counted more than once. Key secondary, exploratory efficacy outcome measures were the proportion of patients with relapses; the annualized rate of relapse; the total number of new gadolinium-enhancing lesions observed on serial T_1-weighted MRI brain scans at weeks 12, 16, 20, and 24 (i.e., lesions persisting for more than 4 weeks were counted only once); and the change from the baseline lesion volume on T_2-weighted MRI scans. Because a reference scan was needed to determine whether a lesion was new, there was no count of new gadolinium-enhancing lesions for the baseline scan.

STATISTICAL ANALYSIS

Eight new gadolinium-enhancing lesions detected on four T_1-weighted MRI scans between weeks 12 and 24 were expected in patients in the placebo group, and it was assumed that the data would follow a negative binomial distribution, resulting in an expected standard deviation of 11.7 for the placebo group. Assuming a 60% reduction in numbers of gadolinium-enhancing lesions detected on T_1-weighted MRI in the rituximab group as compared with the placebo group, it was expected that the mean number of lesions would be 3.2 and the standard deviation would be 4.87, with the standard deviation calculated with the use of the same method. Originally, the

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.

fastcase®
Smarter legal research.