Neurotherapeutic Strategies for Multiple Sclerosis

Teresa C. Frohman, PA-C, MPAS[a,b,*], Shin C. Beh, MD[a], Eric J. Kildebeck, MD, PhD[a,c], Ram Narayan, MD[a], Katherine Treadaway, LCSW, ACP[a], Elliot M. Frohman, MD, PhD[a,d,*]

KEYWORDS

• Multiple sclerosis • Exacerbation • Corticosteroids • Adrenocorticotrophic hormone • Disease-modifying therapy • MS • Pregnancy

KEY POINTS

- Multiple sclerosis is the most common disabling neurologic disease of young adults.
- There are now 16 US Food and Drug Administration–approved disease-modifying therapies for multiple sclerosis as well as a cohort of other agents commonly used in practice when conventional therapies prove inadequate.
- Pregnancy is a state of immunomodulation associated with an antiinflammatory milieu that leads to a reduction in disease activity. The postpartum period has been associated with a resurgence of disease activity.
- An MS exacerbation can be defined as a neurologic event lasting more than 24 hours in the absence of increased body temperature or infection. A Psudo-exacerbation is when the patient experiences a reemergence or deterioration of neurologic deficits, lasting less than 24 hours, and/or occurring in the presence of increased body infection with or without infection (also known as Uhthoffs Phenomenon).

[a] Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA; [b] Department of BioEngineering, University of Texas at Dallas, 800 West Campbell Road, Richardson, TX 75080, USA; [c] Center for Engineering Innovation, University of Texas at Dallas, Institute for Innovation and Entrepreneurship, 800 West Campbell Road, Richardson, TX 75080, USA; [d] Department of Ophthalmology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA

* Corresponding author. Department of Neurology and Neurotherapeutics, University of Texas Southwestern School of Medicine, 5323 Harry Hines Boulevard, Dallas, TX 75235.
E-mail addresses: teresa.frohman@utsouthwestern.edu; elliot.frohman@utsouthwestern.edu

Neurol Clin 34 (2016) 483–523
http://dx.doi.org/10.1016/j.ncl.2016.05.001 **neurologic.theclinics.com**
0733-8619/16/$ – see front matter

INTRODUCTION

The inception of an organization solely dedicated to the investigation and ultimate cure of multiple sclerosis (MS) was set in motion in 1946, when Silvia Lowry established the National Multiple Sclerosis Society after publishing an advertisement she took out in the New York Times, inquiring to the world whether anyone had identified a potential treatment that might be used for her brother, who had a particularly aggressive and accelerated course of the disease.

No affirmative replies were forthcoming in time to shift Sylvia's brother's disease trajectory, and he ultimately succumbed to the disease. As if establishing the National MS Society (which continues to be the most important advocacy organization for the research and treatment of MS worldwide) was not a sufficient individual contribution to the world, Sylvia lobbied Congress in 1950, arguing that the time had come for the government to play a leading role in advancing the understanding of the pathobiological underpinnings of neurodegenerative disorders in general, and for MS in particular.

Through her efforts, the government established the National Institute of Neurological Disorders and Stroke, with the government contributing a mere $14,000 for the investigation of MS before the founding of the institute, whereas since that time Congress has appropriated in excess of $1.5 billion dollars for the investigation of a landscape of neurologic disorders, and in excess of $110 million dollars has been dedicated to MS. The reason for opening this article with this preamble is that it powerfully underscores what is possible, when confronted by one of the most challenging neurologic disorders, before the advent of disease-modifying therapies. Further, this story also emphasizes the impact that even a single individual can have on the process of patient care, education, and discovery. The remainder of this article provides the details on an expanding repertoire of innovative neurotherapeutic capabilities, all of which are derivatives of the scaffolding assembled by Sylvia Lowry.

UNITED STATES FOOD AND DRUG ADMINISTRATION–APPROVED MULTIPLE SCLEROSIS THERAPIES

Table 1 provides a list of common side effects and adverse effects.

Injectables

Interferon-beta

Several clinical trials for interferon-beta (IFNB) have shown significant reductions in clinical and radiologic measures of disease activity and severity; in general, IFNB reduces Annualized relapse rate (ARR) by about one-third and radiologic activity by two-thirds to 90%.[1–10] Intramuscular interferon (IFN)-1a (Avonex) is administered once weekly, subcutaneous IFN-1a (Plegridy) is given every other week, subcutaneous IFNB-1a thrice weekly (Rebif), and subcutaneous IFNB-1b every other day (in our center, we recommend dosing of Betaseron/Betaferon and Extavia 3 times weekly, as with Rebif administration).

Most studies show no significant differences in efficacy among these IFNB products.[11–17] By contrast, the INCOMIN and EVIDENCE trials suggested that high-dose IFNB-1b and high-dose subcutaneous IFNB-1a were slightly superior to low-dose intramuscular IFNB-1a, respectively.[18,19] Despite slightly greater efficacy, higher dose IFNB carries the increased risk of neutralizing antibodies (NABs) and side effects (flulike symptoms, injection site reactions, transaminitis, dysthyroidism, anemia, leukopenia, alopecia, and depression).[11,15–17]