

A New Biotherapeutic Approach for the Treatment of Multiple Sclerosis

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Multiple Sclerosis (MS) is a chronic autoimmune disease of the Central Nervous System (CNS) that affects approximately 400,000 people in the United States [1,2], and presents in several forms with the most prevalent being Relapse-Remitting (RR-MS) that affects nearly 85% of all MS patients. RR-MS is characterized by periods of debilitating disease symptoms followed by extended periods of remission. The second most common form is chronic progressive MS, with approximately 15% of the patients presenting with this form; most RR-MS patients develop progressive disease after several decades. This CNS disorder has no known etiology. However, there is prevalence among populations living in higher latitudes, and exposure to vitamin D by sunlight, or lack thereof, has been suggested as a factor in the development of MS [1]. Statistics show that MS affects white women more than women of color, and that MS afflicts women more than men by a 3:1 ratio [1].

Current Pharmacotherapy

Disease-modifying therapies for RR-MS involve the use of interferon-based immunomodulatory drugs such as glatiramer acetate, fingolimod, teriflunomide and natalizumab, each with its own success rate and list of side effects [2-4]. The goal of these drugs is to prolong the time to relapse and reduce brain lesions. Betaseron is an interferon- β -1b preparation and Avonex and Rebif are interferon- β -1a compounds that are currently available as injectable forms of therapy and show some level of effectiveness at reducing the number of acute exacerbations [5,6]. Nonetheless many patients on extended interferon consumption have significant and severe side-effects including injection site necrosis and liver dysfunction [3,5]. Fingolimod has been shown to be effective against RR-MS, but this drug has additional side effects that necessitate caution in widespread use [7,8]. Natalizumab was found effective for patients with highly active forms of MS that were unresponsive to other MS treatments, however, continued use of the drug resulted in increased risk of multifocal leukoencephalopathy [9]. A number of new oral immunosuppressants including rapamycin and laquinimod have been approved by the FDA, with the mode of treatment being the upregulation of T_{reg} and T_{eff} cells [10].

Each of these drugs requires medically trained personnel for injections, and has unacceptable side effects, and/or limited efficacy. Thus, new disease-modifying therapies that would work alone, or in combination with standard care, are needed. Side-effects, cost of drug, and issues associated with administration often reduce compliance and limit treatment options for MS patients.

New Biotherapy for MS

Over the last decade, there has been a surge in awareness of new treatments for MS that include Low Dosages of Naltrexone (LDN). A website based in the United Kingdom, LDNNow, (<http://www.ldnnow.co.uk>) [11] serves as a reliable source of qualified and peer reviewed knowledge to help patients, family support, clinicians understand this new biotherapeutic approach for treatment of MS and avoid the pitfalls of internet misinformation. The website posts scientific publications, clinical trials, and patient feedback for an expanding population of MS patients taking LDN successfully.

In some ways, the clinical story has preceded the laboratory documentation that LDN is an effective treatment for MS. Internet

conversations suggest that some patients have been on LDN successfully for more than 2 decades. The first reports of LDN use in a laboratory story which facilitated hypothesis-driven, controlled studies were published in 2009. Utilizing an animal model of Experimental Autoimmune Encephalomyelitis (EAE) that is an imperfect model of MS, and treatment that began at the time of induction of disease, it was reported that LDN administered daily to mice diminished clinical disease, and even prevented, behavioral signs of myelin-oligodendrocyte protein (MOG₃₅₋₅₅) (MOG)-induced expression of this progressive form of EAE [12,13]. This novel therapy took advantage of the body's own chemistry and a new biological pathway that has been shown to be effective in the treatment of a variety of disorders and complications thereof (i.e., cancer, diabetes) [14-17].

The underlying biological pathway that is being modulated is the opioid growth factor (OGF) – OGF receptor (OGFr) axis. Research over the last 3 decades has characterized this pathway and elucidated the peptide and receptor involved [18-22]. Blockade of the interaction between OGF and its nuclear-associated receptor OGFr using classical opioid antagonists such as naltrexone (NTX) or naloxone have been used to decipher the function of this pathway [14,23]. Complete blockade resulting from systemic injections of high dosages of NTX or multiple dosages of low levels of NTX over a 24-hr period continuously blocks the receptors and accelerates cell proliferation and growth [23]. Intermittent or short-term opioid receptor blockade (e.g., 4-6 hr each day) by the use of LDN inhibits cell proliferation and growth during the interval when the opioid antagonist is no longer present [23].

The contrary responses to different dosages of NTX are related to the pharmacological action of opioid antagonism and duration of receptor blockade [14]. Hence, the response to receptor blockade is a compensatory upregulation of both peptide and receptors, but with complete blockade (i.e., high dosages) there is no opportunity for interaction. However, studies have shown that low dosages of NTX (i.e., LDN) which block the receptors for short periods (i.e., 4-6 hr daily in rodents) [12,13] have an additional 18-20 hr when the elevated endogenous opioids and receptors can interface and cause exaggerated responses. In the case of the endogenous OGF, this is reduced cell proliferation.

Using the mouse model of EAE, blockade of the interaction of OGF with its nuclear-associated receptor, OGFr, represses clinical signs of the disease. Mice immunized with MOG and randomized to receive either LDN or saline demonstrated that 100% of the mice receiving saline developed EAE, whereas only two-thirds (68%) of mice receiving LDN ever presented with behavioral symptoms; 23% of those mice with

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EAE receiving LDN exhibited remission (no behavior signs of disease for 2 consecutive days) [12,13].

The feedback loop that activates LDN is the secretion and action of the endogenous opioid OGF. Direct administration of this non-toxic, pentapeptide also minimized progression of progressive EAE [24] when given at the time of disease induction or at the time of established disease [25], a more clinically relevant model. The specific targets and pathways that OGF uses to repress cell division have been outlined [20-28], and many *in vitro* (tissue culture) reports on normal or cancer cell lines document that OGF acts directly on the OGFr to inhibit cell proliferation [15,16]. The action is reversible, non-apoptotic, and independent of the immune system, other than inhibiting inflammatory T cells following immunization [27-29]. Based on *in vitro* and *in vivo* studies using human cancer cell lines and nude mice, OGF or LDN can be combined effectively with standard chemotherapeutic agents for an additive or enhanced repression of tumor progression [23]. Although no studies have been conducted using EAE models, there is no reason for combinatorial therapy to be ineffective.

Although the mouse model for progressive EAE is more consistent and reliable, approximately 85% of patients present with RR-MS, and thus this demands laboratory studies using the RR-EAE model. SJL mice injected with proteolipid protein develop RR-EAE within 2 weeks of immunization. Over the course of 2 months, the mice demonstrate between 2 and 4 relapses following the initial flair of disease, with corresponding remissions [30]. Laboratory studies on endogenous opioids and RR-EAE are limited, but evidence presented at scientific venues suggests that OGF treatment initiated at the time of disease induction was successful at preventing relapses following the initial flair. Moreover, the peak disease was subdued and neuropathological evaluation demonstrated that OGF repressed proliferation of microglia, astrocytes, and T lymphocytes [30].

Clinical Trials on LDN for Relapse-remitting Multiple Sclerosis

A few randomized trials on LDN have been published with a majority of the outcomes being based on increased quality of life for patients with RR-MS or secondary progressive MS [31,32]. In all cases, LDN was reported to be a safe therapeutic option, and larger trials of longer duration are warranted.

Drug Toxicity

Unlike many of the FDA- approved compounds such as Rebif and fingolimod that have been shown to impose significant toxicity issues [2,8], neither LDN nor OGF have been associated with toxicity or apoptosis. Because the concentrations of naltrexone are well below physiological levels, and the stimulated secretion of OGF, which is a neuropeptide that is normally produced and secreted, and rapidly metabolized, by the body, substantial adverse effects have not been noted. The action of exogenous and endogenous OGF is reversible, non-cytotoxic/non-apoptotic inducing, not associated with differentiation, migration, adhesion, or invasion, and occurs at physiologically relevant concentrations [e.g.,15,26-28]. OGF activity is not cell-, tissue-, or organ-specific [19], is targeted to the cyclin-dependent inhibitory kinase pathway in the G₀/G₁ phase of the cell cycle [20], and influences overall tissue organization.

Summary

The story of the use of endogenous opioids as a novel pathway for treatment of MS has a profile that includes clinic to lab bench and back

to clinic. Following up on numerous anecdotal conversations about the efficacy of LDN for treatment of MS and other autoimmune disorders, hypothesis driven, controlled laboratory studies were initiated to delineate the underlying mechanisms of how LDN works as a novel therapy for autoimmune disorders such as MS. Despite the widespread usage and internet support for a broad-based population of people with different forms of MS, as well as varied therapeutic experiences, LDN, and its active ingredient OGF, working at the OGFr site are now recognized as the pathway. This bench to bedside story on opioids and treatment of autoimmune diseases already holds promise for translational medicine, as many people with MS are benefitting from the availability of a low-cost, non-toxic, oral therapy in LDN.

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