

## Lipoic Acid—A Novel Therapeutic Approach for Multiple Sclerosis

a report by

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Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that has its symptom onset primarily in young and middle-aged adults. Approximately 400,000 Americans are affected by this chronic and disabling disease, with a significant burden placed on the affected person and his or her family, the healthcare system, and society. MS was described as a clinicopathological entity in the mid-19th century, but significant progress in understanding its pathogenesis has been made only in the past few decades. It is now well established that a dysregulated immune system that targets CNS myelinated tissue including brain, spinal cord, and optic nerves causes MS. Inflammation, focal demyelination, and axonal and neuronal loss are prominent features of the pathology. What triggers the autoimmune response is still not understood. However, our understanding of the pathogenesis of MS has led to the development of treatments that alter the course of the disease.

Until 1993 there were no US Food and Drug Administration (FDA)-approved drugs for MS. Recombinant interferon beta 1b (Betaseron®) became the first disease-modifying treatment available for the illness. Since then, five other FDA-approved drugs have become available for MS treatment. These include two forms of recombinant interferon beta 1a (Avonex®, Rebif®), glatiramer acetate (Copaxone®), mitoxantrone

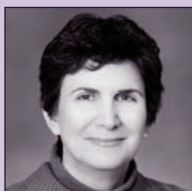
(Novantrone®), and natalizumab (Tysabri®). The interferons and glatiramer acetate work by modulating the immune system and lead to upregulation of the anti-inflammatory response and downregulation of the pro-inflammatory response in MS. Mitoxantrone is a chemotherapy agent that kills the T and B cells and temporarily halts the pro-inflammatory response. Natalizumab, a specific monoclonal antibody to alpha 1 integrin molecule (VLA-4), reduces the ability of activated T cells to cross the blood-brain barrier (BBB). All of these medications reduce disease activity in MS, although none is curative. Despite the availability of these six drugs, there remains a significant need for additional drugs for MS. The use of currently available drugs is limited in that all are available only as injections, are expensive, and can cause significant side effects. Therefore, there is considerable interest in the development of safe oral treatments for MS.

Lipoic acid (LA) is a naturally occurring antioxidant that is available as an over-the-counter dietary supplement in the US. LA as a therapy for diabetic neuropathy has been evaluated in several clinical trials.<sup>1-4</sup> LA is available in oral as well as intravenous formulations in Germany for the treatment of diabetic neuropathy. LA has also been tested as an effective therapy for an animal model of MS, and a phase I trial of LA has been completed in MS.<sup>5,6</sup> This article will review the current data that provide a rationale for assessing the efficacy of LA in MS.



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### Biochemical Properties of Lipoic Acid

LA is an eight-carbon compound containing two sulfur atoms in a dithiolane ring structure (1,2-dithiolane-3-pentanoic acid; thioctic acid) (see *Figure 1A*).<sup>7</sup> Originally thought to be a vitamin, it was later found that both eukaryotic and prokaryotic cells are able to synthesize LA *de novo*. LA is readily absorbed from the diet, thereby making oral administration a viable therapeutic option. Commercially available LA is usually a racemic mixture of R enantiomer- $\alpha$ -LA and S-enantiomer of  $\alpha$ -LA (rac- $\alpha$ -LA). LA can be administered orally and intravenously and is rapidly absorbed and taken up by cells, where it is reduced to dihydrolipoic acid (DHLA), with which it forms a redox couple (see *Figure 1B*).

LA protects the cell from free radicals that result from intermediate metabolites or from the degradation of exogenous molecules and from heavy metals, thus functioning as a potent antioxidant. LA also has a significant role in cellular carbohydrate metabolism. In its R-form, LA serves as a co-factor for five mitochondrial proteins that have a central role in oxidative metabolism when covalently bound to a lysine residue (lipoamide; lipoyllysine); these five proteins are the acyltransferase component of the pyruvate complex,  $\alpha$ -ketoglutarate, the branched-chain  $\alpha$ -ketoacid dehydrogenase complexes, pyruvate

dehydrogenase complex, and the glycine cleavage system. As an antioxidant, LA can be reduced to its redox partner, DHLA, which is a powerful reducing agent and important in the regeneration of endogenous antioxidants such as glutathione. Importantly, LA can act as a metal chelator, a scavenger of ROS, and is able to repair damage from oxidative stress. This antioxidant effect and role of LA in carbohydrate metabolism has made it a very appealing potential drug in diseases such as diabetic neuropathy, MS, and Alzheimer's disease, where oxidative damage is presumed to play a pathogenic role.<sup>8,9</sup>

### Multiple Sclerosis Is an Inflammatory Disease of the Central Nervous System

Inflammation due to a dysregulated immune system plays a pivotal role in MS pathogenesis. The etiology of this inflammatory response is unknown, but once activated the T and B cells, macrophages, adhesion molecules, and soluble mediators of inflammation such as cytokines play significant roles in causation and propagation of the disease.

### Matrix Metalloproteinase-9, Adhesion Molecules, and Cytokines in Multiple Sclerosis

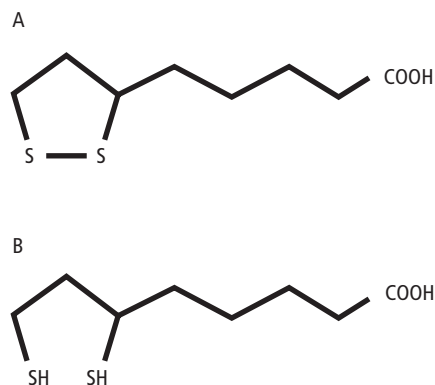
The transmigration of activated immune cells across the BBB plays a significant role in MS pathogenesis as it leads to the development of new inflammatory lesions in MS.<sup>10,11</sup> Initially, activated T cells roll along the endothelial layer via reversible binding via selectins and their ligands. Pro-inflammatory T-cell cytokines such as tumor necrosis factor (TNF)- $\alpha$  and interferon (IFN)- $\gamma$  further induce the expression of cellular adhesion

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molecules on the endothelial cells, particularly ICAM-1 and VCAM-1, permitting a tight binding of the T cells to the endothelial cells via their ligands on the surface of T cells, lymphocyte-function-associated antigen (LFA)-1, and very late antigen (VLA)-4, respectively.<sup>12–15</sup> Activated T cells produce a variety of chemokines, cytokines, and proteases that promote transmigration across the BBB. Chemokines such as macrophage inflammatory protein (MIP)-1 $\alpha$  and cytokines such as IFN- $\gamma$  increase the avidity of T-cell binding to the endothelial cells and direct transendothelial migration of the T cells.<sup>16</sup> MMPs are also produced by these activated pro-inflammatory T cells, particularly MMP-9, which enzymatically disrupt the subendothelial membrane and extracellular matrix components, allowing the ingress of T cells into the CNS parenchyma.<sup>17–21</sup>

Clinical trials have suggested that serum mean MMP-9 levels are increased in MS patients with clinical and magnetic resonance imaging (MRI) disease activity and that a shift in MMP-9/TIMP-1 balance toward proteolytic activity of MMP-9 could be relevant in MS immune dysregulation,<sup>22</sup> whereas the MMP-9/TIMP-1 ratio in serum showed higher ( $p=0.04$ ) values in stable relapsing–remitting MS (RRMS) than primary progressive (PP) but also in active patients, evaluated either clinically ( $p=0.006$ ) or from the MRI

**Figure 1: Chemical Structures of Lipoic Acid (A) and Its Redox Partner Dihyrolipoic Acid (B)**



( $p<0.05$ ), compared with inactive disease.<sup>23</sup> In addition, increased serum levels of sICAM-1 have been associated with inflammatory disease activity and with the appearance of gadolinium enhancing lesions on brain MRI.<sup>24–26</sup> Studies have shown that upregulated adhesion molecules in blood and serum could indicate ongoing inflammation in the CNS in MS subjects.<sup>27,28</sup>

The role of cytokines in MS pathogenesis is evident by correlations that exist between expression of pro-inflammatory cytokines during periods of clinical worsening and of regulatory cytokines during periods of clinical remission.<sup>29</sup> Increased levels of pro-inflammatory cytokines such as TNF- $\alpha$ , IFN- $\gamma$ , and interleukin 2 (IL-2) have been found in the peripheral blood, CSF, and brain lesions of MS patients.<sup>30–35</sup> Anti-inflammatory cytokines that include IL-4 and IL-10 are expressed during remission. Numerous reports document the association between these pro-inflammatory cytokines and disease activity, thus implicating them as mediators of immunopathogenesis in MS.<sup>30,31,33,36</sup>

### Macrophages and Oxidative Injury in Multiple Sclerosis

In addition to the role of T and B cells in MS pathogenesis, activated macrophages and microglia also play a significant role in tissue destruction as well as repair.<sup>37</sup> Macrophages produce pro-inflammatory enzymes such as proteases, lipases, and cytokines and special molecules such as osteopontin that destroy tissues in a variety of ways. In addition, macrophages are a source of reactive oxygen and nitrogen species, thus causing oxidative damage.

Therapeutic agents that target adhesion molecules and MMP-9 may prove useful as treatments for MS and other neurological diseases in which migration of inflammatory cells plays a pathogenic role.<sup>38–43</sup> A growing body of literature exists that demonstrates the ability of LA to reduce the expression of surface adhesion molecules on endothelial cells, suppress MMP-9 activity, and inhibit the trafficking of inflammatory cells across the BBB.<sup>5,6,44–46</sup> Taken together, these data provide evidence for the further evaluation of LA as a therapeutic agent in MS.

### Animal Model of Multiple Sclerosis—Experimental Autoimmune Encephalomyelitis

As a widely used model of MS, experimental autoimmune encephalomyelitis (EAE) has provided important insights into the immunopathogenesis of MS and led to the development of new therapeutic

approaches for treating MS.<sup>43,47</sup> EAE can be induced in a variety of animal species, including mice, rats, and rhesus macaques.<sup>48,49</sup> EAE in Swiss/Jackson Laboratory (SJL) mice is characterized by an acute episode of paralysis followed by recovery and then spontaneous relapses of paralysis. This chronic relapsing model of EAE is similar to relapsing–remitting MS, which is the clinical pattern that is most frequently seen in patients at the time of their initial diagnosis.<sup>49</sup> Secondary progressive MS is represented best by the C57BL/6 EAE model; this form of MS is seen in many patients following relapsing–remitting disease. EAE in C57BL/6 is characterized by acute paralysis from which mice do not recover followed by a slow clinical worsening without relapse. Similar to MS patients, histopathological examination of spinal cords from mice with EAE reveals multifocal areas of demyelination with axonal loss in the spinal cord associated with inflammatory infiltrates composed of lymphocytes and macrophages.<sup>49</sup>

### Lipoic Acid and Experimental Autoimmune Encephalomyelitis

LA suppresses and treats EAE in the SJL mouse model.<sup>5</sup> When administered prior to disease onset, LA successfully suppressed the clinical course of EAE in a dose-dependent fashion (25–50–100mg/kg/day), with complete suppression achieved at 100mg/kg/day over a 45-day treatment period. Importantly, when LA was administered after the onset of the disease, the clinical severity of EAE greatly diminished. Histopathological examination of spinal cords from mice that received LA revealed a significant reduction in inflammatory infiltrates and axonal damage. The ability of LA to suppress and treat EAE in a second mouse model (C57BL/6 mice immunized with MOG 35-55 peptide) and in a rat model of EAE has been confirmed by others.<sup>6,46</sup>

LA inhibits MMP-9 activity directly and at the level of transcription. Moreover, LA was shown to inhibit migration of the human Jurkat T cell line across an extracellular matrix barrier *in vitro*.<sup>45</sup> *In vitro*, immunohistochemical staining of spinal cords from mice treated with LA revealed a reduction in the expression of adhesion molecules VCAM-1 and ICAM-1 from the surface of endothelial cells.<sup>44</sup> Similar studies have demonstrated that LA reduces EAE in rats in part by reducing the permeability of the BBB and decreasing the migratory capacity of monocytes to enter the CNS.<sup>46</sup>

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In addition, LA has also been reported to induce the generation of cyclic adenosine monophosphate (cAMP) in human T-cells and natural killer (NK) cells in a concentration-dependent fashion.<sup>50,51</sup> Pharmacological inhibitors of the EP2 and EP4 prostanoid receptors blocked the ability of LA to stimulate the generation of cAMP, suggesting that LA may be acting as an agonist of these G-protein coupled receptors. In the presence of LA, IL-12/IL-18-induced secretion of IFN- $\gamma$  by NK cells was significantly decreased. In addition, using a lactate dehydrogenase release assay, it was demonstrated that pre-treatment with LA significantly diminished the ability of NK cells to

lyse target K562 cells. It is thought that a subset of NK cells may contribute to the disease severity observed in MS. These findings suggest that LA may modulate the activation and function of NK cells and that in the presence of LA NK cells may become less pathogenic. Taken together, these data suggest that in addition to its direct effects on oxidative stress as an antioxidant, LA may have non-antioxidant properties that are therapeutic in EAE and MS.<sup>52</sup>

### Clinical Trials

A single clinical trial of LA in MS patients has taken place.<sup>53</sup> This was a placebo-controlled, double-blind, randomized phase I trial that looked at the safety and tolerability of different doses of oral LA. In addition, this study explored the pharmacokinetics (PK) of LA and the effects of LA on serum immune markers, including MMP-9 and sICAM-1, after two weeks of LA

Further studies to better understand the mechanism of action of lipoic acid are under way.

administration. The study included 37 MS subjects who were randomly assigned to one of four groups: placebo, LA 600mg twice a day, LA 1,200mg once a day, or LA 1,200mg twice a day. Subjects received the study drug for 14 days. The PK sera were collected at eight time-points. The first blood draw was just before taking the first dose of the study drug, followed by collections at 15, 30, 60, 120, 180, and 240 minutes and 24 hours after ingestion of the first dose of study drug. Maximum serum concentration of LA ( $C_{max}$ ) correlated with dose and varied considerably among subjects. Subjects who took 1,200mg LA had substantially higher  $C_{max}$  levels (range 0–19 $\mu$ g/ml) than those taking 600mg LA (range 0–3.7 $\mu$ g/ml).

Authors also explored the effects of LA  $C_{max}$  on the levels of serum MMP-9. The baseline MMP-9 levels were obtained prior to patients receiving the study drug. Subsequent MMP-9 levels were measured at three additional time-points. These included 24 hours after the study initiation (visit three of study), at one week (visit four of study), and at the end of two weeks (visit five) of the study. The outcome measure was the mean change in MMP-9 levels compared with baseline and visits three, four, and five. A significant negative correlation between the LA  $C_{max}$  values and the MMP-9 mean change (Kendall's tau=0.263;  $p \leq 0.04$ ) was observed.

The outcome measure was to evaluate the relationship between LA and serum sICAM-1 levels with the mean change between visits three, four, and five compared with baseline sICAM-1. Those subjects who took higher doses of LA showed the greatest decrease in sICAM-1 (Jonckheere-Terpstra test;  $p=0.03$ ), suggesting a significant dose–response relationship between LA dose and the mean change in sICAM-1.

Safety data revealed that high-dose LA was generally safe and well tolerated. Nausea, mild gastrointestinal discomfort, and strange odor in the urine were minor complaints of some subjects in the study. One subject developed a reversible disseminated maculopapular allergic rash with fever that required discontinuation of LA.

Since LA made by various manufacturers is available over the counter and drug manufacturing is not regulated by the FDA, it is critical that we have rigorous PK studies that validate various LA formulations. Yadav and colleagues have recently completed a detailed PK study looking at three different formulations of 1,200mg of oral LA that shows that there are differences in PK parameters of LA made by different manufacturers (unpublished data). This study shows that there remains considerable variability in the PK parameters between subjects (unpublished data).

Thus, the single published clinical study on MS shows that high-dose oral LA is safe, reasonably tolerated, and capable of reducing serum MMP-9 and sICAM-1 levels.<sup>53</sup> Whether similar results can be seen in subsequent

studies needs to be determined. Based on EAE studies and the preliminary results from this clinical trial, LA appears to have a potential of a useful drug in treating MS.

### Conclusion

Based on the EAE work, LA appears to be an effective anti-inflammatory therapeutic agent. A preliminary clinical trial in MS patients demonstrated that high-dose LA administration is safe. Larger phase II/III clinical trials are warranted to assess the clinical efficacy of LA in MS. Further studies to better understand the mechanism of action of LA are under way. The use of oral LA as a potential treatment for MS will be a major breakthrough in MS therapeutics. ■

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