RESEARCH ARTICLE

Suppression of Multiple Sclerosis by Ultraviolet Light

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ABSTRACT

The inverse relationship of multiple sclerosis to sunlight exposure was proposed at least 50 years ago but conclusive evidence is unavailable. Since the proposal was made, many researchers have jumped to the conclusion vitamin D mediates this effect. Vitamin D is a pro-hormone produced in the skin by ultraviolet irradiation and/or sun exposure. In addition, an inverse relationship between plasma levels of the vitamin D metabolite, 25(OH)D$_3$, and a reduced incidence of multiple sclerosis has been noted. As a result of the relationship clinical trials have been carried out to determine if vitamin D supplementation can suppress the disease. The results have not supported this idea. In an animal model of multiple sclerosis (experimental autoimmune encephalomyelitis) the vitamin D hypothesis was refuted. Ultraviolet irradiation, on the other hand, consistently reduces the incidence and severity of experimental autoimmune encephalomyelitis. Because experimental autoimmune encephalomyelitis is a widely accepted model of human multiple sclerosis, clinical trials testing the efficacy of the narrow band ultraviolet light in suppression of multiple sclerosis appear warranted. If in fact this narrow band light does suppress human multiple sclerosis, isolation and identification of the compound produced by this light should be initiated.
Introduction:

Multiple sclerosis (MS) is one of a number of diseases classified as an autoimmune disease. The initiator(s) of MS is not known, but multiple risk factors have been identified including reduced sunlight exposure \(^1\). Sunlight is comprised of predominantly (99%) ultraviolet light which can be further subdivided into UVA, UVB and UVC (Figure 1) \(^2\). UVC is largely absorbed by the ozone layer and has the highest energy. UVA has the lowest energy but, nearly all of it reaches the earth and is not removed by glass or clouds. UVB lies in the middle with higher energy but is readily filtered by regular glass and clouds. It is UVB that has the most pronounced effect on changing the course of multiple sclerosis, at least in a mouse model of MS \(^3\). A brief summary of current and emerging therapies for multiple sclerosis will be presented. This review will also discuss the possible role of segments of UV light in the suppression of MS. The original observation of sun exposure as a risk factor for MS will be covered as well in this review. A literature review was completed using the following search terms: “uv light” AND “multiple sclerosis”, “uv” AND “multiple sclerosis”, “uv light” AND “EAE”, “uv” AND “EAE”, “sunlight” AND “multiple sclerosis” and “sunlight” AND “EAE” within PubMed. Additional relevant work was also considered from citations within the manuscripts identified using the described search terms.

Figure 1. Sunlight produces primarily UV radiation. When UVB is not filtered out, it will produce vitamin D in skin. Using a lamp that predominantly produces energy at 311 nm provides protection against EAE without changing circulating levels of 25(OH)D.

Types of multiple sclerosis:

Multiple sclerosis is a chronic debilitating autoimmune disease that attacks the myelin sheath protecting the brain, spinal cord and optic nerves. The body can repair the damage, but not without causing scarring or sclerosis. There are two types of multiple sclerosis: 1. relapsing remitting and 2. primary progressive \(^4\). The majority (85%) of individuals suffer from relapsing remitting MS. Individuals with this disease type have periods of time when the symptoms disappear or dissipate (remission). Those suffering from the primary progressive form of the disease do not go into remission but can have periods of low or inactive...
disease. Eventually, patients with relapsing remitting disease will enter a progressive phase similar to those diagnosed with primary progressive disease, and are then classified as having secondary progressive MS. Most (80%) MS patients first experience neurological inflammation or demyelination resulting in vision problems or tingling in extremities, lasting at least 24 hours before full diagnosis of multiple sclerosis occurs. This is called clinically isolated syndrome (CIS). The recognition of this early risk factor by regulatory authorities opens the door for testing disease-modifying agents very early in the development of the disease.

**Demographics of MS**

Worldwide estimates of people living with this disease is 2.8 million. Over 700,000 adults are living with multiple sclerosis in the US. There are nearly 3 times as many women than men suffering this disease. The incidence is much higher in the northern half of the US. Most individuals are diagnosed between the ages of 20 and 40 and live on average 6-7 years less than people without MS. Those diagnosed later in life typically have primary progressive disease, whereas children and younger adults suffer relapsing remitting disease. On average individuals with MS live for ~30 to 40 years at an estimated cost of treatment of $90,000/year.

**Multiple sclerosis therapies**

Despite recognition of multiple sclerosis as a disease since the middle of the 19th century, it was only about 30 years ago that the first drug, interferon beta-1b, was approved by the FDA for treatment. There are now nearly 20 drugs approved for MS. These therapies reduce relapse rates and slow progression, but do not reverse or prevent completely disease progression. Some therapies have very undesirable side effects. Emerging therapies include B cell depletion such as Rituximab. It is an anti-CD20 monoclonal antibody originally approved for the treatment of B cell lymphoma but shows some promise in the treatment of MS. Inhibitors of a tyrosine kinase known as Bruton’s tyrosine kinase (BTK) also show promise. Inhibiting BTK leads to modulation of B cell activities without depletion of the cell population and thus, mitigating some obvious off-target effects. Therapies targeting later stage disease include simvastatin, a statin and ibudilast, an inhibitor of cyclic nucleotide phosphodiesterases. Phase 2 trials testing both these drugs in MS patients with secondary progressive disease demonstrated reduced brain atrophy.

**Vitamin D and MS**

Vitamin D is another compound that has been extensively studied as a possible therapy for MS. Investigation of vitamin D for MS treatment was prompted by the finding that individuals living further from the equator have a higher risk of getting MS. This observation was first noticed in the 1960’s in Europe, but this latitudinal relationship has since been shown throughout most of the world and extended to include not only incidence but also severity of disease. UV radiation is much higher at the equator and since UV also produces vitamin D, vitamin D was proposed as the mediator of the protective effect. In support of this idea, MS patients have lower circulating levels of 25(OH)D3, the major metabolite of vitamin D. Whether the depressed 25(OH)D3 levels are a cause, or a consequence of the disease is not known, however. Several clinical trials have been completed to determine if vitamin D can suppress MS, but to-date the results have been inconclusive at best and most meta-analyses do not support the idea of using vitamin D as a therapy for MS patients. One larger clinical trial initiated nearly 10 years ago is still on-going (NCT01817166). The study is designed to test vitamin D in preventing progression from CIS to MS and is placebo-controlled. Data obtained with animal models of MS (discussed below) do not support the idea that vitamin D therapy can have any impact on the disease without associated hypercalcemia. To avoid hypercalcemia, vitamin D itself as opposed to the active hormone, i.e. 1 alpha, 25-dihydroxy vitamin D have been tested in MS patients. However high dose vitamin D without associated hypercalcemia have led to some cases of worsening disease. Two studies, one unreported and one still in progress, are attempting to address this concern (NCT01490502 and NCT03610139). It appears unlikely that vitamin D or its active form 1,25-dihydroxy vitamin D can be used to suppress MS.

Interestingly, a large (n = 25,871 subjects) randomized, placebo-controlled study (VITAL trial) recently completed in the vitamin D field to assess the effect of vitamin D supplementation in the prevention of cancer and cardiovascular disease showed a reduced incidence in autoimmune disorders. These patients were provided with a daily vitamin D supplement of 2000 IU for 5 years. This finding is very surprising for several reasons: the population was not deficient in vitamin D, the average age of the subjects was 67 years, and there were equal number of men and women in the study population. Most autoimmune disorders begin before 50 years of age, and more women than men typically get autoimmune diseases. Furthermore, the data generated to-date would...
strongly suggest only those individuals deficient in vitamin D are likely to benefit in any way from supplementation. It should also be noted that only a single case of multiple sclerosis was reported in this study population. Since most clinical trials do not support the idea of a beneficial effect of vitamin D supplementation in MS patients coupled with the possibility of worsening conditions, the VITAL trial results should not be used to encourage additional trials. The resources should be directed towards the idea that UV light independent of vitamin D may suppress MS.

A commonly used preclinical animal model of multiple sclerosis is the experimental autoimmune encephalitis (EAE). In this model mice or rats are injected with a myelin basic protein peptide together with Complete Freund's adjuvant, inactivated mycobacteria and pertussis toxin. This model has been successfully utilized to identify therapies currently prescribed for MS patients. One of the first preclinical studies testing vitamin D in EAE showed a strong protective effect (Figure 2). However, in this study, hypercalcemia was evident in the mice receiving 1,25(OH)2D3, the hormonal form of vitamin D, and subsequent studies showed elevated calcium is the protective effector of this action of vitamin D2 at least in females. More recent studies conducted in EAE show that UV, specifically a very narrow band of UVB radiation, can suppress the onset and disease severity in wild-type C57Bl6/J mice as well as those that lack the receptor necessary for vitamin D action. Furthermore, mice that lack the ability to produce vitamin D in the skin when exposed to UV light still experience delayed onset and reduced disease severity when subjected to narrow band UVB. These results are consistent with the lack of clinical evidence that vitamin D supplementation can prevent or suppress MS and should direct researchers to focus on other possible mediators of UV in suppression of MS.

**Figure 2.** Summary of in vivo evidence indicating UV’s action in multiple sclerosis is separate from the vitamin D pathway.

<table>
<thead>
<tr>
<th>Agent Administered</th>
<th>EAE Mouse Model</th>
<th>Beneficial?</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D hormone or 1,25(OH)2D3</td>
<td>Yes, but increases blood calcium</td>
<td>Lemire JM, Acher DC. 1,25-dihydroxyvitamin D3 prevents the in vivo induction of murine experimental autoimmune encephalomyelitis. Journal of Clinical Investigation. 1991;87(3):1103-1107.</td>
<td></td>
</tr>
<tr>
<td>Narrow Band UVB</td>
<td>Yes, no need to produce vitamin D in the skin</td>
<td>Irving AA, Marling SJ, Seeman J, Plum LA, DeLuca HF. UV light suppression of EAE (a mouse model of multiple sclerosis) is independent of vitamin D and its receptor. Proceedings of the National Academy of Sciences. 2019;116(45):22552-22555.</td>
<td></td>
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Targets of UV action

Molecular mechanisms underlying the benefit of UV light on EAE remain undefined, although several proposed mechanisms exist. Wang et al. found a general decrease in cytokines in the spinal cord following UV treatment and the reverse in the skin and spleen. A chemokine known as CCL5/RANTES was also found to be decreased in the spinal cords of UV-treated animals. This chemokine has been shown to be important in leukocyte infiltration and is present in the active lesions of MS patients. The depression of this chemokine by UVB in the spinal cord is consistent with a decrease in the lesions of psoriatic patients treated with UVB. Another group has provided some evidence that an antimicrobial peptide, β-defensin-14, may have a role. Mice injected with this UV-inducible peptide prevented development of the disease and also reduced disease severity in mice that were given the peptide after clear clinical scores were evident. More recently, the sphingosine pathway has been implicated in playing a role in UV-mediated protection. Sphingosine-1-phosphate (S1P) is increased by UV irradiation (~92% UVA and ~8% UVB) in the lymph nodes. S1P acts as a chemoattractant causing T-lymphocytes to move from the blood to skin-draining lymph nodes. These results in mice are corroborated with findings in CIS patients where increases in circulating T-cells were observed after exposure to narrow band UVB. Several drugs based on this pathway are currently marketed for MS treatment. Another potential target for explaining the UV suppression of multiple sclerosis is the folic acid pathway. Folates are found in the skin and upon UV irradiation form various pertinent derivatives. Interestingly, the degradation of folic acid is most effective with UVB as opposed to UVA. UVA is much less effective at reducing EAE incidence or severity. It has been noted that macrophages express folate receptors upon activation. One synthetic folate-aminopterin derivative has been tested in animal models of both relapsing-remitting as well as progressive forms of EAE and found to be effective. Another candidate molecule proposed to play a role in UV mediated protection of MS is urocanic acid. Trans-urocanic acid found in the skin absorbs UV to form cis-urocanic acid. Cis-urocanic has been shown to have several immunomodulatory roles and is reduced in the blood of MS patients. However, it was tested for activity in the EAE mouse and shows no protection against the disease. Whether one, or several of these potential UV targets is responsible for the UVB mediated protection observed in animal models of EAE remains to be determined, but this area should continue to be intensively explored. The need for new therapies with less detrimental side effects is high and understanding the mechanism of UV action should provide more opportunities for designing precise therapies.

Clinical trials using UV in MS patients

To-date, only two very small clinical trials have been completed to assess the effectiveness of UVB light in suppressing MS. The first trial was completed in 9 patients suffering from relapsing-remitting disease for an average of 13 years. They were administered narrow band UV light 5 days/week for six weeks. Eighteen to twenty-four weeks after the UV exposure stopped, MRI’s and neurological examinations were completed neither of which showed any changes from baseline. A more recent study was conducted in patients with clinically isolated syndrome. Again, the number of patients was very small and the treatment for only 8 weeks, and at a frequency of 3 times per week. Interestingly, 3 out of 10 patients receiving phototherapy did not convert to multiple sclerosis while all 9 of the patients in the non-treatment arm did. Unfortunately, the results are preliminary and did not confront the gender effect in the disease. These results and the evidence generated in the EAE model strongly support the initiation of a larger study to test the effectiveness of narrow band UV light provided daily to prevent the development of MS.

Conflicts of Interest Statement: LAP has no conflicts of interest to report. HFD serves as a consultant for Cytokind.

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References:


40. Irving AA, Marling SJ, Seeman J, Plum LA, DeLuca HF. UV light suppression of EAE (a mouse model of multiple sclerosis) is independent of vitamin D and its receptor.


