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Cutaneous Side Effects of First/Second Line Oral Disease - Modifying Treatments in Patients with Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a progressive autoimmune and sometimes disabling disease of the central nervous system (CNS), characterized by formation of white matter lesions in the CNS due to inflammation, demyelination and axonal loss. Disease-modifying treatments (DMTs) are being investigated as a treatment choice in patients with MS. Teriflunomide, fingolimod and dimethyl fumarate are the most popular oral forms of the DMTs that are used usually for relapsing forms of MS (RMS), the most common disease phenotype. In this complementary, we have compiled the reports about cutaneous adverse reactions associated with oral first or second line DMTs. There have been recently published rare cases to point out serious cutaneous adverse effects associated with fingolimod therapy such as Kaposi sarcoma, peripheral vascular adverse effects, ecchymotic angioedema-like cutaneous lesions, lymphomatoid papulosis. There are also a few case reports about cutaneous adverse effects of teriflunomide, such as eczema, rash and palmar pustular psoriasis. In addition, a recently published case report has demonstrated another serious adverse effect associated with teriflunomide; drug – induced bullous pemphigoid. However, there aren't many reported skin changes associated with dimethyl fumarate use in patients with MS, just a newly reported case report about transient hair loss. By examining the specific clinical, pharmacological and safety features of all drugs, we tried to provide an overview. In addition, it is important to point out some immunosuppressants may trigger autoimmune diseases. These DMTs may also have led to similar autoimmune phenomenon, attending to the development of some cutaneous autoimmune reactions. The molecular mechanisms behind these reactions are still unknown and further studies are needed to reveal them.

Keywords: Multiple Sclerosis, Teriflunomide, Fingolimod, Dimethyl fumarate, Cutaneous adverse effects

Multiple sclerosis (MS) is a progressive autoimmune and sometimes disabling disease of the central nervous system (CNS), characterized by formation of white matter lesions in the CNS due to inflammation, demyelination and axonal loss [1-3]. However, the disease also affects gray matter as well as white matter, and possibly this effect is related to irreversible disability and progressive symptoms. MS is the second most common cause of disability in young adults. It appears as a result of genetic and environmental factors that serve as activators of the immune response. The age of onset is generally between the mid to late 20s, while the female/male ratio is about 3:1 [4-6].

When the pathophysiology of the disease is reviewed, the migration of inflammatory cells to the CNS, through the blood-brain barrier, shows the first mechanism of disease formation. This inflammation causes white matter lesions or plaques and usually these white matter lesions tend to be noticeable in highly myelinated areas. The most common affected areas are optic nerves, periventricular and subcortical white matter and descending traces in the pons, and midbrain. The spinal cord is also often affected. Depending on their location in the CNS, these lesions typically manifest as symptomatic 'attacks' and indicate 'active' disease [7-9]. Since MS plaques can occur in a variety of neuroanatomic locations, patients may be presented with a wide variety of symptoms. Patients usually report problems related to ambulation, weakness, sensory loss, loss of balance, fatigue, depression, memory loss and urination. However, MS is a very heterogeneous disease. Each patient with a diagnosis of MS may behave differently and the severity of the disease may alter in wide intensity [10].

Disease-modifying treatments (DMTs) are being investigated as a treatment choice in patients with MS [11]. Their effect in reducing CNS damage has been proved with lots of clinical trials so far [1]. Teriflunomide, fingolimod and dimethyl fumarate are the most popular oral forms of the DMTs that are used usually for relapsing forms of MS (RMS), the most common disease phenotype [1]. In approximately 85 % of all cases, MS initially manifests as RMS, which is characterized by episodes of neurological worsening followed by partial or total recovery [1,3]. DMTs, all of which have immunomodulatory or immunosuppressive properties, have shown efficacy to improve the course of RMS [12]. Early DMT therapy has been recommended to control clinical and subclinical inflammatory disease activity [13], but new treatment-related risks have also arisen, including immune - related cutaneous side effects, such as drug induced bullous pemphigoid [14]. The various efficacy and safety profiles of DMTs put more emphasis on 'personalized' approaches that adapt treatment decisions to the patient's disease characteristics and preferences [15]. Although all of the mentioned DMTs act through variable immunological mechanisms, all improve the course of RMS as assessed by reductions in annualized relapse rate and MRI outcomes [13]. Before using fingolimod in the treatment of RMS, the disease was treated with injectable drugs. Next, two other oral agents, teriflunomide and dimethyl fumarate were approved for the treatment of RMS.

Fingolimod is the first oral agent approved by the United States Food and Drug Administration (2010) and European Medicines Agency (2011) for maintenance therapy of relapsing–remitting multiple sclerosis. It is a modulator of S1P (sphingosine-1-phosphate) receptor, which is located on the surface of lymphocytes and CNS cells. After phosphorylation, fingolimod phosphate, which is its active form, binds to the S1P receptor. Then, it inhibits the outflow of lymphocytes from the lymph nodes, causing the lymphocytes to redistribute. This redistribution reduces infiltration of pathogenic lymphocytes into the CNS. However, it reduces the potential of the abnormal autoimmune processes to occur. Furthermore, this molecule may also cross the blood-brain barrier and bind to S1P receptors on CNS cells. As a result of lymphocyte retention, the number of peripheral blood lymphocytes decreases during fingolimod therapy. The lymphocyte counts become normal within 1 to 2 months after cessation of treatment. This indicates that the existing effect is reversible and allows the redistribution of lymphocytes to lymphoid tissues [16,17]. The risk-benefit profiles of fingolimod have been specified in one phase II study [18], three phase III studies and in a long-term follow-up study [19-21]. In addition, post-marketing clinical experience is still being shared. The most common adverse events related to fingolimod (incidence ≥10% and > placebo) found in various clinical trials are headache, influenza, diarrhea, nausea, cough, back pain and elevation of liver enzymes [22]. However, first dose bradycardia or atrioventricular block formation due to fingolimod use are known in some patients, hence vital signs and electrocardiograms must be monitored clinically before and after the first dose is administered. Apart from the first dose effect of the drug, there are also some other well-known side effects associated with fingolimod including QT interval prolongation, hypertension, macular edema, pulmonary toxicity, and possibly hepatotoxicity. It is also important to point out that 18 patients treated with fingolimod have developed progressive multifocal leukoencephalopathy, including 3 patients without prior natalizumab exposure [23,24]. Although some certain adverse events exist among the patients including some cardiac abnormalities, macular edema, some hepatic laboratory abnormalities and possible infection risks, there have been recently published rare cases to point out serious cutaneous adverse effects associated with fingolimod therapy such as Kaposi sarcoma [25], peripheral vascular adverse effects [26], ecchymotic angioedema-like cutaneous lesions [27], lymphomatoid papulosis [28]. Fingolimod has increased the risk of varicella zoster virus infection compared to placebo in clinical trials. Fatal disseminated varicella zoster virus [29] and herpes simplex virus-1 infections [30] have occurred. Cryptococcal central nervous system and skin infections have also been reported [31,32]. There is also a temporal association between fingolimod exposure and immune thrombocytopenic purpura (ITP), however dose–effect association or pathogenesis is still unclear [33]. Furthermore, skin cancers including basal cell carcinoma, squamous cell carcinoma and melanoma have been reported in the clinical trials [21,34].

Teriflunomide is the second oral agent approved by the United States Food and Drug Administration (2012) and European Medicines Agency (2013) for maintenance therapy of relapsing–remitting multiple sclerosis. The drug reversibly inhibits dihydro-orotate dehydrogenase, an enzyme in de novo pyrimidine synthesis and facilitates a contrary effect on proliferation of activated T and B lymphocytes [1] limiting their contribution to MS pathogenesis [1]. Oral daily therapy of Teriflunomide has shown efficacy on disability, annualized relapse rate, and magnetic resonance imaging markers of disease in patients with RMS, and in those with a first clinical episode of suggestive MS [35-38]. The safety analysis of teriflunomide-treated patients was obtained from three placebo-controlled trials: TEMSO, TOWER, and TOPIC [35-37]. Adverse events reported in 10 % of patients treated with teriflunomide were diarrhea, nausea, increased alanine aminotransferase, headache and hair thinning [39]. Minor reductions in white blood cells have been observed in patients receiving teriflunomide in clinical trials. No increase in the incidence of serious infections has been observed with teriflunomide. There has been no

increased risk of malignancy with teriflunomide treatment. Peripheral neuropathy, including both polyneuropathy and mononeuropathy has been reported. There aren't many reported skin changes associated with teriflunomide use in patients with MS. Only one life-threatening gross skin change has been reported so far; a patient with toxic epidermal necrolysis (TEN) [40]. There are also a few case reports about cutaneous adverse effects of teriflunomide, such as eczema, rash and palmar pustular psoriasis [40-43]. In addition, a recently published case report has demonstrated another serious adverse effect associated with teriflunomide; drug – induced bullous pemphigoid [14]. Totally five cases of teriflunomide associated cutaneous drug reactions can be found in literature search via PubMed. Psoriasiform changes were mentioned in 2 of the cases after drug use. The other associated skin changes were drug – induced bullous pemphigoid, nail loss and toxic epidermal necrolysis. Considering recently reported skin reactions associated with teriflunomide, neurologists and patients should be aware of warning signs and symptoms that might be associated with a cutaneous drug reaction caused by this drug.

Dimethyl fumarate is the third oral agent approved by the United States Food and Drug Administration (2013) and European Medicines Agency (2014) for maintenance therapy of relapsing–remitting multiple sclerosis. Dimethyl fumarate has been studied for its effects since 1959 [44]. The exact mode of action of this drug remains a topic of discussion, but it is known that dimethyl fumarate acts on the nuclear factor-like-2 (Nrf2) pathway and has immunomodulatory effects [45]. The efficacy and safety of dimethyl fumarate were investigated in two large randomized, placebo-controlled Phase III studies DEFINE and CONFIRM. These studies confirmed the efficacy of dimethyl fumarate on relapse rates, and only one of them confirmed it effect on progressive disability [46,47]. It is a safe and efficient drug with no reported increased risk of infection, including opportunistic infections and no increased risk of malignancy. The most common adverse effects are gastrointestinal symptoms and flushing. These placebo-controlled Phase III studies have also demonstrated that flushing occurred in 40% of patients and caused discontinuation in 3% of them. On the other hand, gastrointestinal effects such as abdominal pain, diarrhea and nausea, occurred in approximately 12-18% of patients. Furthermore, an elevation in the level of hepatic enzymes, increased proteinuria, leukopenia and progressive multifocal leukoencephalopathy were observed [48]. There are also some recent reports about newly noticed rare adverse effects of this drug, including articular and musculoskeletal pain [49]. There aren't many reported skin changes associated with dimethyl fumarate use in patients with MS, just a newly reported case report about transient hair loss [50]. In addition, it is important to point out that this drug is nowadays being used for the treatment of dermatological diseases such as psoriasis and bullous pemphigoid [51,52].

We have compiled the reports about cutaneous adverse reactions associated with oral first or second line DMTs. Some of the reports are recently published, thus they may not have created sufficient awareness among neurologists yet. By examining the specific clinical, pharmacological and safety features of all drugs, we tried to provide an overview. In addition, it is important to point out some immunosuppressants may trigger autoimmune diseases. The dysregulation of the immune system with

Drugs	**Cutaneous Side Effects**
Fingolimod	Kaposi sarcoma [25], peripheral vascular adverse effects [26], ecchymotic angioedema-like cutaneous lesions [27], lymphomatoid papulosis [28], disseminated varicella zoster virus [29], herpes simplex virus-1 infections [30], cryptococcal skin infections [32], immune thrombocytopenic purpura [33], skin cancers (basal cell carcinoma, squamous cell carcinoma and melanoma) [21, 34]
Teriflunomide	Drug – induced bullous pemphigoid [14], toxic epidermal necrolysis [40], nail loss [42], palmar pustular psoriasis [43], psoriasiform changes of fingernails [41]
Dimethyl Fumarate	Transient hair loss [50]

Table: Cutaneous side effects of first/second line oral disease- modifying treatments.

inactivation of regulatory T-cells and stimulation of B-cell clones can be suggested as the main determining factor that leads to the emergence of autoimmune diseases [53,54]. These DMTs may also have led to similar autoimmune phenomenon, attending to the development of some cutaneous autoimmune reactions. To summarize, considering recently reported skin reactions associated with these drugs, neurologists and patients should be aware of warning signs and symptoms. The molecular mechanisms behind these reactions are still unknown and further studies are needed to reveal them.

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