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Review

What's new about oral treatments in Multiple Sclerosis? Immunogenetics still under question

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ABSTRACT

Multiple Sclerosis (MS) is a chronic pathology affecting the Central Nervous System characterized by inflammatory processes that lead to demyelination and neurodegeneration. In MS treatment, disease modifying therapies (DMTs) are essential to reduce disease progression by suppressing the inflammatory response responsible for promoting lesion formation. Recently, in addition to the classical injectable DMTs like Interferons and Glatiramer acetate, new orally administered drugs have been approved for MS therapy: dimethyl fumarate, teriflunomide and fingolimod. These drugs act with different mechanisms on the immune system, in order to suppress the harmful inflammatory process. An additional layer of complexity is introduced by the influence of polymorphic gene variants in the Human Leukocyte Antigen region on the risk of developing MS and its progression. To date, pharmacogenomic studies have mainly focused on the patient's response following admission of injectable drugs. Therefore, greater consideration must be made to pharmacogenomics with a view to developing more effective and personalized therapies.

This review aims to shed light on the mechanism of action of the new oral drugs dimethyl fumarate, teriflunomide and fingolimod, taking into account both the importance of immunogenetics in drug response and pharmacogenomic studies.

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1. Introduction

Multiple Sclerosis (MS) is a chronic disimmune disease of the Central Nervous System (CNS) characterized by demyelination and neurodegeneration, which affects approximatively 2.5 million people worldwide. This disease is the most common cause of permanent physical disability in young adults, with an onset between 20 and 40 years [1], displaying a greater prevalence in women (3:1) [2].

Like other chronic neurological disorders, MS represents a serious health problem. Many neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), are characterized by progressive dysfunction of the nervous system, with neuroinflammation often making an important contribution to the neurodegenerative course [3]. Rather, in MS inflammation plays a central role.

MS is a complex disease and its pathogenesis involves different mechanisms including demyelination, neurodegeneration, and inflammatory phenomena, leading to the formation of plaques localized both in the white and in the grey matter of the CNS [4].

MS is not only a physically disabling disease, but it also affects the cognitive ability of the patients [5]. The symptoms are heterogeneous and depend on the location of the demyelinated area within the CNS [1,6]. The disease course is highly variable, although two main types are recognizable: relapsing-remitting MS (RRMS) and progressive MS (PMS) [7].

MS treatment consists of administrating immunomodulating agents to postpone and reduce the risk of relapses. Specifically, an acute treatment using corticosteroids is important to decrease the relapses duration, while disease modifying therapies (DMTs) are long-term treatments essential to suppress the inflammatory response that promotes lesions formation, thus reducing disease progression [8]. Typically, DMTs are used for patients with RRMS [9], where patients with a mild or moderate active disease start the therapy with a first-line DMT, whereas patients with an aggressive form of the disease start with a second-line DMT [10]. Notably, patients treated with a first-line DMT that do not show an effective response, are switched to a second-line DMT. Classical MS first-line treatments include the use of Interferons (IFNs) and Glatiramer acetate (GA), two injectable drugs that reduce the annual relapse rate by approximately 30% [11].

In recent years, the number of drugs that can be used in the treatment of MS has increased. The new orally administered drugs approved for MS treatment, dimethyl fumarate, teriflunomide (first-line treatments) and fingolimod (second-line treatment), offer new therapeutic options. In this review we will focus on the above-cited orally administered drugs and their mechanism of action, and will additionally examine their efficacy in the context of immunogenetics.

1.1. Insights on MS: from genetics to environmental factors

Several genetic and environmental factors influence the risk of developing MS. However, although the environment seems to play a role in terms of disease progression [12,13], the aetiology of this pathology is still poorly understood.

The majority of the genetic risk factors are related to the immune system, more specifically, the HLA (Human Leukocyte Antigen) region. This genomic region of about 4000 kb is located on the short arm of chromosome 6, and includes more than 200 highly polymorphic genes that are divided into three classes [14]. The HLA-DRB1*15:01 allele continues to represent the major genetic risk factor for MS, with an odds ratio (OR) of 3.08 [15]. In addition, other polymorphisms have been associated with MS, such as HLA-A*02:01, which is considered a protective allele for MS risk [16]. Moreover, our research group has recently described two polymorphisms, HSP70-2 +1267 A/G (rs1061581) and HSP70-HOM +2437 T/C (rs2227956), that are related to the risk of developing MS [17,18]. However, several environmental factors may contribute to disease susceptibility, including vitamin D deficiency, infections and smoking [12]. Interestingly, MS prevalence increases at higher latitude and its distribution seems to be influenced by sunlight exposure – solar light is the principal factor for the production of vitamin D_3. Vitamin D deficiency, due to a reduced exposure to solar light, is therefore a possible risk factor for the development of MS [19]. Vitamin D acts as an important immuno-modulating factor influencing the transcription of several immune-related genes, and thus the differentiation of immune system cells [20]. Smoking is another factor that may affect both the risk of developing MS and the disease progression [21]. In recent years, attention has been focused on the gut and its microbiota, which is important for the proper function of the immune system [22]. Different factors, such as diet, medications or stress, can alter the gut microbiota, leading to gut inflammation and alterations of intestinal immunity [23]. In particular, diet can alter the commensal gut microbiota and also affect cellular metabolism, with consequences for the immune system [24]. Within this context, an association between obesity and a higher risk of developing MS has been demonstrated [25], where the accumulation of white adipose tissue may lead to a systemic inflammation [26].

Epigenetic mechanisms also seem to play a role in MS, promoting a pro-inflammatory phenotype and influencing demyelination and remyelination processes. In this regard, different environmental agents, such as Epstein-Barr virus, smoking and diet, are able to induce epigenetic modifications, thus contributing to the development of the disease [27,28].

2. Focus on oral treatments for MS

2.1. Dimethyl fumarate

Dimethyl fumarate (DMF) is a first-line oral drug for the treatment of RRMS, approved by the FDA in 2013 [29]. Fumaric acid esters, including DMF, have been previously employed for the management of psoriasis.

After administration, DMF is metabolized at gut level to produce the active compound monomethyl fumarate (MMF), that is