Journal of Chromatography B, 1019 (2016) 15–20

Contents lists available at ScienceDirect

Journal of Chromatography B

journal homepage: www.elsevier.com/locate/chromb

Role of dimethyl fumarate in oxidative stress of multiple sclerosis: A review

Suneetha A.[a,*], Raja Rajeswari K.[b]

[a] Department of Pharmaceutical Analysis, Hindu College of Pharmacy, Amaravathi Road, Guntur 522 002, Andhra Pradesh, India
[b] College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur 522510, Andhra Pradesh, India

ARTICLE INFO

Article history:
Received 23 June 2015
Received in revised form
19 December 2015
Accepted 5 February 2016
Available online 8 February 2016

Keywords:
Multiple sclerosis
Oxidative stress
Dimethyl fumarate

ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory disease of the CNS affecting both white and grey matter. Inflammation and oxidative stress are also thought to promote tissue damage in multiple sclerosis. Recent data point at an important role of anti-oxidative pathways for tissue protection in chronic MS, particularly involving the transcription factor nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2). Thus, novel therapeutics enhancing cellular resistance to free radicals could prove useful for MS treatment. Oxidative stress and anti-oxidative pathways are important players in MS pathophysiology and constitute a promising target for future MS therapy with dimethyl fumarate. The clinical utility of DMF in multiple sclerosis is being explored through phase III trials with BG-12, which is an oral therapeutic agent. Currently a wide research is going on to find out the exact mechanism of DMF, till date it is not clear. Based on strong signals of nephrotoxicity in non-humans and the theoretical risk of renal cell cancer from intracellular accumulation of fumarate, post-marketing study of a large population of patients will be necessary to fully assess the long-term safety of dimethyl fumarate. The current treatment goals are to shorten the duration and severity of relapses, prolong the time between relapses, and delay progression of disability. In this regard, dimethyl fumarate offers a promising alternative to orally administered fingolimod (GILENYA) or teriflunomide (AUBAGIO), which are currently marketed in the United States under FDA-mandated Risk Evaluation and Mitigation Strategy (REMS) programs because of serious safety concerns. More clinical experience with all three agents will be necessary to differentiate the tolerability of long-term therapy for patients diagnosed with multiple sclerosis. This write-up provides the detailed information of dimethyl fumarate in treating the neuro disease, multiple sclerosis and its mechanism involved via oxidative stress pathway. The rapid screening methods are also need to be developed to estimate DMF in biological samples to perform and proceed for further investigations.
© 2016 Elsevier B.V. All rights reserved.

1. Introduction

Multiple sclerosis (MS) is a demyelinating, chronic inflammatory immune-mediated disease of the central nervous system (CNS), which begins most often in young adults and is more than twice as common in women as in men [1,2]. MS is characterized either by episodic acute periods of exacerbations (relapses or attacks), gradual progressive deterioration of neurologic function, or combinations of both. MS is classified into four independent subtypes or forms: relapsing-remitting (RR), primary progressive (PP), secondary progressive (SP), and progressive relapsing (PR); the former is the most prevalent form and accounts for approximately 85% of all cases [3]. The etiology of MS is still not entirely known, although it is strongly believed that both genetic and environmental components play a central role in disease onset and development [4,5]. Neuro degeneration in multiple sclerosis (MS) is a multi factorial process manifesting from the very onset of the disease [6,7]. While, in the early stages of MS, neuro degeneration is mainly driven by inflammation [8], later in the course of the disease several interacting factors are involved. Among well known and less well-documented players, mitochondrial dysfunction seems to have a crucial role [9,10]. Mitochondrial changes in MS include altered distribution and structure, together with biochemical and molecular abnormalities [9,11–14]. Mitochondrial damage is caused by several factors, including oxidative stress [15–19]. Oxidative stress can arise in a biological environment whenever there is an imbalance between reactive oxygen species (ROS) production and the cell's buffering capacity; this imbal-

* Corresponding author.
E-mail address: drasuneetha@gmail.com (S. A.).

http://dx.doi.org/10.1016/j.jchromb.2016.02.010
1570-0232/© 2016 Elsevier B.V. All rights reserved.

ance results in oxidation of proteins, lipids, and DNA [14,20]. ROS are natural bioproducts of oxidative phosphorylation [14,21] but can also be generated by activated inflammatory cells, including macrophages and microglia [22–24]. Just as activated macrophages and microglia are an important source of ROS, oxidative stress can, in turn, activate key factors (such as nuclear factor k Beta) that upregulate proinflammatory gene expression [25]. Thus, an autotoxic loop is sustained [26]. Accordingly, studies of oxidative stress in MS have dramatically increased in recent years [5,27,28].

Multiple sclerosis (MS) is a disease of unknown cause with multiple factors implicated in its pathophysiology [29–31]. There is growing evidence of the involvement of oxidative stress in neural damage in MS [31–34]. Because of the high lipid content in neural tissue, oxidative stress, with its associated increased free radical production, leads to lipid peroxidation [35]. At present there is no established biomarker for investigating lipid peroxidation and oxidative stress in MS. Isoprostanes are a class of lipid peroxidation products that are generated when free radicals attack the arachidonic acid esterified in phospholipid pools of cell membranes [35–39]. 8-isoprostaglandin F2α (8-isoPGF2α) is one of the most abundant and well-recognized isoprostanes and is now recognized as a gold-standard biomarker for in vivo oxidative stress and lipid peroxidation [38–41]. Oxidative stress may contribute to the disease mechanisms in both the relapsing-remitting and progressive phases of MS through its involvement in inflammation and axonal degeneration, respectively. Increased lipid peroxidation in MS leads to an increase in the markers of oxidative stress, but there is also a depletion of the antioxidant reserves as reported in a study of patients with MS [42]. There have also been some reports of evaluation of the relative production of 8-isoPGF2α in biological fluids, mostly in serum, urine and CSF in patients with MS [43–49]. Treatments that address symptom management and treatments that change the course of the disease by modifying the number and severity of attacks and the progression of disability. Acute exacerbations are usually treated with short-term, powerful steroids or muscle relaxants, whereas prevention of relapses and progressive nerve damage has traditionally relied on the interferons such as Betaseron (interferon β-1b), Avonex (interferon β-1a) and Rebif (interferon β-1a). The exact mechanism by which the interferons slow disease progression is unknown, but clinical study results suggest that they may down regulate certain inflammatory cytokines, inhibit T-cell proliferation and/or reduce blood-brain barrier permeability and T-cell migration into the CNS. Avonex and Rebif are generally used as primary therapies (first-line), while Betaseron is reserved as a second-line agent. A fourth non-interferon agent, Copaxone (glatiramer acetate), has also been available for some time, but it is generally reserved for patients who fail interferon therapy. Copaxone acts by suppressing the immune system's attack on myelin and thus decreasing the frequency and severity of attacks. Monoclonal antibodies such as Tysabri (natalizumab) are also being used for MS treatment as they works by blocking the receptors on white blood cells that allow them to enter the brain and spinal cord and thus leading to a decrease in inflammation (Note: Tysabri was once withdrawn from US market due to side effect risks (progressive multifocal leukoenncephalopathy), but was again reintroduced in 2006). Immuno suppresants such as Novantrone act by slowing down the disease progression and lessen the number of relapses through their ability to suppress the activity of T cells and B cells. Exacerbation management is done using corticosteroids like prednisone, prednisolone, methylprednisolone, betamethasone, and dexamethasone that act by shortening the duration of acute attacks by lessening the swelling and inflammation in MS lesions.

Dimethyl fumarate (TECFIDERA) is an orally administered fumarate ester recently FDA approved for first-line monotherapy in early stage of multiple sclerosis. Because it is rapidly and completely hydrolyzed by esterases before reaching the systemic circulation, the pharmacologic activity of dimethyl fumarate (DMF) is due to its active metabolite, monomethyl fumarate (MMF) [50]. DMF and MMF structures are represented in Fig. 1.

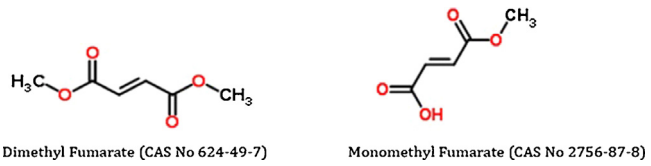

Fig. 1. Chemical Structures of DMF and MMF.

Although the precise mechanism of action is incompletely characterized, monomethyl fumarate is thought to exert neuroprotective effects in patients with multiple sclerosis by activating the nuclear erythroid 2-related factor 2 (nuclear factor erythroid-derived 2-like 2; Nrf2) [51] transcriptional pathway [50,52–54]. Using a model of endogenous neuronal oxidative stress, Albrecht, et al., studied time and concentration-dependent effects of dimethyl fumarate and monomethyl fumarate and concluded that dimethyl fumarate causes a brief period of oxidative stress that results in the intra neuronal synthesis of the antioxidant glutathione (GSH) mediated through the Nrf2 pathway [55]. Others have proposed additional immuno modulatory actions for dimethyl fumarate mediated through nitric oxide, interleukins, tumor necrosis factor (TNF-α), or other cytokines [56–60]. Two randomized, controlled, phase 3 clinical trials DEFINE [61] and CONFIRM [62] of dimethyl fumarate administered at a dose of 240 mg twice daily by mouth over a period of 2 years were associated with a statistically significant reduction in clinical disease exacerbations (the primary efficacy endpoint), a reduction in the necessity for rescue therapy with intravenous corticosteroids, and improvements in other indicators of disease progression, including MRI images of brain lesions. To date studies have been insufficiently powered to detect a consistent effect on disability progression, [54] but quality of life assessments are expected as a secondary outcome measure of the 5-year follow-on study (ENDORSE) [63]. The main metabolite of DMF is MMF (monomethyl fumarate) leads to direct modification of DMF is also used in the treatment of psorasis as antiinflammatory agent and other diseases, such as necrobiosis lipoidica, granuloma annulare, and sarcoidosis were also found to respond to treatment with DMF in case reports or small patient series.

2. Oxidative stress in MS

Oxidative stress is generated by the inability to detoxify or to repair the resulting damage caused by the generation of reactive oxygen species (ROS) like superoxide (O_2^-), hydrogen peroxide (H_2O_2) or hydroxyl radicals (·OH). A dysbalance in the physiological redox state of a cell may thus lead to toxic effects via production of peroxides or free radicals that damage sub-cellular structures including proteins, lipids, and DNA. Further, some reactive oxidative species have the capacity to act as intracellular messengers in redox signaling cascades thus interfering with normal cellular signaling pathways. Additionally, reactive nitrogen species (RNS) are a family of toxic molecules derived from nitric oxide (•NO) and superoxide (O_2^-) produced via the enzymatic activity of inducible NO synthase 2 (NOS2) and NADPH oxidase, respectively. In concert, these molecules may eventually lead to oxidation or nitrosylation finally resulting in cellular damage, associated with cell death and subsequent organ dysfunction. Oxidation is an important component of the inflammatory process and increased antioxidant activity appears to be anti-inflammatory [64,65]. MS is caused when immune system cells attack the myelin sheath that surrounds nerve fibres in the brain and spinal cord. In addition to its pro-

Download English Version:

https://daneshyari.com/en/article/1211879

Download Persian Version:

https://daneshyari.com/article/1211879

Daneshyari.com