Pharmacological Reports 69 (2017) 702–708

Contents lists available at ScienceDirect

Pharmacological Reports

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

Review article

Mechanism of action of three newly registered drugs for multiple sclerosis treatment

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ARTICLE INFO

Article history:
Received 10 October 2016
Received in revised form 16 January 2017
Accepted 16 February 2017
Available online 22 February 2017

Keywords:
Multiple sclerosis
Dimethyl fumarate
Teriflunomide
Alemtuzumab

ABSTRACT

Multiple sclerosis (MS) is a disease of suspected autoimmune origin leading to neurodegeneration. The disease pathomechanism is considered to be primarily based on neuroinflammation directed against myelin antigens caused by autoreactive T cells. MS etiology remains still unknown, which makes it difficult to create an efficient therapy, therefore, MS treatment targets mechanisms involved in disease pathology. In this review, we present the mechanism of action of three newly registered drugs for MS. Dimethyl fumarate (DMF) is an agent presenting a broad spectrum of action. Its main activity is based on activating the nuclear factor E2 dependent pathway leading to antioxidant enzyme synthesis. DMF in general suppresses the pro-inflammatory immune activity and exerts a neuroprotective action. Teriflunomide is a more focused drug, acting as an inhibitor of pyrimidines synthesis, important for rapidly dividing cells such as activated lymphocytes. Similarly, alemtuzumab, an anti-CD52 antibody, causes depletion of mainly lymphocytes. Since in MS pathology, T and B cells are involved, this mode of action is promising.

Contents

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http://dx.doi.org/10.1016/j.pharep.2017.02.017

Multiple sclerosis and its treatment

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) of multifactorial etiology, combining genetic and environmental factors [1,2]. The disease usually affects young people, with a peak of onset between 20 and 40 years old and women more often than men. MS is a significant cause of disability, especially in people in their most productive working and childbearing years [3]. MS is characterized by demyelination and axonal loss starting from the dysregulation of the immune system followed by a neurodegenerative process. In the pathogenesis both immune-mediated and neurodegenerative processes play a crucial role, however, the link between these two elements is under debate. Axonal damage is considered critical for permanent deficits in the progressive form of MS but the precise mechanisms of axonal injury remain unclear. Currently available therapies focus on preventing ongoing inflammation in the CNS, which may provide neuroprotection to some extent. None of the currently approved disease-modifying drugs protect neurons and axons from neurodegeneration. There is still a challenge of understanding and measuring neuroprotection at the axonal and neural levels [4–6].

MS is still not a curable disease, however, since interferons (IFNs) were first registered in 1993, some therapeutic progress has been achieved. Many other drugs were introduced to the market, including natalizumab, fingolimod, and a new preparation of old drugs such as pegylated form of IFN-beta-1a (peg-IFN-β-1a). The majority of them are available to treat the most typical form of the disease which is relapsing-remitting multiple sclerosis (RRMS) or alternatively secondary progressive MS with neurological exacerbations (known as relapsing-progressive MS – RPMS). Until now, the progressive form of the disease is a great therapeutic challenge and is still an unmet need of affected patients [7].

In 2013 and 2014, the European Medicine Agency approved three drugs for MS which are dimethyl fumarate, teriflunomide (a metabolite of leflunomide) and alemtuzumab. The first two are used orally and are considered as first-line treatment, the third one, due to its safety profile is considered as second-line or even third-line treatment. It is interesting that all three drugs were originally used for alternative indications including fumarate derivatives for psoriasis, leflunomide for rheumatoid arthritis, and alemtuzumab for chronic lymphatic leukaemia. The mechanism of action of the new drugs in MS is of great interest and still not fully described.

In Poland, a national MS therapeutic programme is available. It gives the opportunity to use first-line drugs which are: interferons, glatiramer acetate and recently dimethyl fumarate available from 1 July 2016. The second-line therapy includes natalizumab and fingolimod.

There is much interest in new MS therapeutic agents, however, the majority of published data focuses on the results of clinical trials [8]. Although during the past few decades there was a better understanding of the basic pathophysiology of the disease, the exact mechanism of action of even well-established therapy is not fully elucidated and little is known about the newly registered drugs [9]. The aim of the current publication is to review the published data on preclinical studies on the possible mode of action of these three recently accepted drugs.

Dimethyl fumarate

Dimethyl fumarate (DMF), the orally administered drug is the ester of fumaric acid metabolized in the gastrointestinal tract by esterases. After gastric digestion, DMF metabolites (methylhydrogen fumarate – MHF and others), but not DMF, are detected in the blood and are probably responsible for the clinical effect of DMF [10–12]. DMF was first used in psoriasis treatment, as the immunomodulating agent [13,14]. Since psoriasis is an autoimmune disease based on similar pathomechanisms as MS, the idea arose to use DMF for MS treatment.

General anti-inflammatory activity

The first experiments on the DMF mode of action were made in the topic of psoriasis treatment. Important data were obtained by de Jong et al. [15], who observed that the DMF main metabolite, monomethyl fumarate (MMF), influences the peripheral blood mononuclear cells (PBMC) and T cells, enhancing their IL-4 and IL-5 production, even after stimulation. This is the evidence of switching the Th1-dependent immune response towards Th2-dependent that could also be beneficial in MS treatment, since it is a Th1-mediated disease. Similarly, in the experiments involving psoriasis patients, there is evidence that DMF causes a decrease in the number of circulating lymphocytes, especially CD8+ [16], and induces the apoptosis of activated T cells *in vitro* and monocyte-derived dendritic cells [17,18].

Studies performed on animals with experimental allergic encephalomyelitis (EAE), an animal model of MS, revealed that oral administration of DMF or its metabolites ameliorates the disease course. When combined with the widely used interferon therapy, a further improvement was observed [19]. DMF administered to animals with EAE increases the levels of anti-inflammatory plasma cytokines (IL-5, IL-10) [20]. Experiments conducted both on mice with EAE, and PBMCs isolated from psoriasis patients, confirmed the hypothesis about influence of DMF on dendritic cells (DCs) diffrentiation. Results showed that DMF treatment results in generation of type II DCs, that produce IL-10, but not IL-12 or IL-23. Furthermore, IL-10 promotes Th0 cells polarization into Th2 subtype, while IL-12 and IL-23 would promote polarization into Th1 and Th17 respectively. Induction of Th2 cells eventually results in anti-inflammatory cytokines production and attenuation of ongoing EAE/MS [21].

There is strong evidence that DMF inhibits the activity of nuclear factor κB (NF-κB) – transcription factor regulating the inflammatory response. It was shown that MMF in lipopolysaccharide (LPS)-induced cell culture of monocyte-derived DCs reduced the activation of NF-κB [22]. Activity inhibition is due to blockage of nuclear translocation, not the DNA binding. In normal human dermal fibroblasts stimulated with tumor necrosis factor (TNF-α), DMF inhibited the nuclear translocation of NF-κB p50 subunit [23], while in human endothelial cells no effect of DMF on NF-κB binding to DNA was noted [24].

Antioxidant action

The best known and widely described effect of DMF is its antioxidant activity. For diseases based on autoimmune-derived inflammation, anti-oxidative agents are very desirable. A number of studies showed that DMF and its metabolites activate the Nrf2-dependent (nuclear factor E2) intracellular pathway leading to an increase in antioxidant enzymes expression [25,26]. Nrf2 is a cytoplasmatic protein, in basal state coupled with Kelch-like ECH-associated protein 1 (Keap1) protein. Keap1 acts as a suppressor of Nrf2 and as an intracellular sensor of the redox state. Nrf2 bound to Keap1 undergoes ubiquitination and degradation. Oxidative stress modifies the thiols in cysteine residues in Keap1 resulting in the release of Nrf2 and its translocation into the nucleus. In the nucleus, Nrf2 makes heterodimers with MAF proteins, whose accumulation eventually increases the transcription of ARE (antioxidant response elements) regulated genes in the promoter region for genes encoding the second phase antioxidant enzymes. Those enzymes are, among others glutathione-S-transferase (GST),