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Review

Mode of action and clinical studies with fumarates in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) as a chronic neuro-inflammatory and neurodegenerative disease of the central nervous system is frequently associated with severe disability and impairment in quality of life.
Early disease-modifying treatment options have mainly focused on inflammatory aspects of the disease. Recently, the neurodegenerative features have received more attention in experimental models, paraclinical assessments and the evaluation of drug effects. Fumaric acid esters (FAEs) as orally available immunomodulatory and neuroprotective compounds have thus advanced to a highly interesting MS treatment option.
Here, we will review the pharmaceutical history of FAEs, their immunomodulatory and putative neuroprotective mechanisms of action and clinical trial data in relapsing MS.

Contents

Introduction

In contrast to several other neuroimmunological disorders with involvement of the central nervous system (CNS), multiple sclerosis (MS) is a commonly occurring disease with prevalence estimates up to more than 200 per 100,000 in distinct regions of Europe (Kingwell et al., 2013).

MS is frequently associated with disability that demands management of various symptoms including spasticity, ambulation, bladder and sexual symptoms, fatigue and cognition (Thompson et al., 2010). This impacts quality of life and working capacity and results in high socioeconomic burden of the disease (Flensner et al., 2013). Yet, variability of disease courses (Lublin and Reingold, 1996), gender and geographical distribution (Evans et al., 2013; Kingwell et al., 2013) underscore the heterogeneity of MS which is so far not well explained.

Consensus exists about an autoimmune pathology finally composed of both inflammatory and neurodegenerative features. Importantly, the latter seem to be a distinct characteristic of the disease itself (Hafler et al., 2005; Hohlfeld and Wekerle, 2004). Mechanisms may include oxidative stress and both axonal and neuronal damage (Hafler et al., 2005; van Horssen et al., 2011).

Yet, both treatment of relapses via steroids (Burton et al., 2012) or plasma exchange techniques (Koziolek et al., 2012; Magana et al., 2011; Schroder et al., 2009) and early disease-modifying treatment options (beta-interferons, glatiramer acetate) (Comi et al., 2001, 2009; Jacobs et al., 2000; Kappos et al., 2006) focused on inflammation via immunomodulation and/or immunosuppression (e.g. mitoxantrone) (Hartung et al., 2002).

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The concept of neuroprotection has recently attracted more attention and has been evaluated on both (para-)clinical (e.g. MRI, optical coherence tomography (OCT)) and experimental level for different substances (reviewed by Stroet et al., 2013).

Fumaric acid esters (FAEs) were initially used in the treatment of an immunological skin disorder — psoriasis. Because of their potent anti-inflammatory effects, they have been introduced in MS. Their further investigation revealed not only anti-inflammatory, but also putative neuroprotective mechanisms of action which made them a highly interesting treatment option for MS.

We will here review the history, the preclinical data on FAEs and the relevant data of clinical MS trials with FAEs, especially with regard to safety and efficacy aspects.

History of fumarates

By the end of the 1950s the German chemist Schweckendiek topically applied FAEs on his own psoriatic lesions as he assumed an underlying metabolic disorder of the citric acid cycle which may be restored by FAE supplementation (Schweckendiek, 1959). Extending this approach, he swallowed oral FAEs and subsequently these drugs were offered to patients with psoriasis, yet on an off-label basis.

More than 30 years later, two double-blind trials were performed in psoriasis (Altmeyer et al., 1994; Nieboer et al., 1990). These resulted in the approval of Fumaderm®, an oral mixture of dimethyl fumarate (DMF) and ethylhydrogen fumarate (EHF), for the treatment of severe therapy-refractory psoriasis in Germany in 1994 (Mrowietz et al., 1999).

This compounded fumarate was then used in a pilot study on ten patients with relapsing–remitting MS (RRMS) and MRI activity (Schimrigk et al., 2006). Although three patients withdrew, significant results on MRI outcome parameters (number and volume of gadolinium-enhancing lesions) were shown. In general, the safety profile of Fumaderm® was favorable in this study. Yet gastrointestinal side effects and flushing — known from dermatological populations — diminished the tolerability of the drug.

The advancement to "BG12" is composed of only DMF and different galenics to improve tolerability. This compound has been further evaluated on the experimental level and in clinical trials.

Preclinical data on DMF and its mode of action

DMF is the di-methylester of fumaric acid and chemically named trans-1,2-ethylenedicarboxylic acid dimethyl ester. Intestinally localized esterases cleave DMF to monomethyl fumarate (MMF), the main active metabolite that is absorbed and distributed including passage of the blood–brain-barrier. Yet, there is data on faster, but short-lived activity of low concentrations of DMF with both anti-inflammatory and anti-oxidative effects (Albrecht et al., 2012).

After metabolism in the citric acid cycle, MMF is eliminated primarily via exhalation and only to small extents via urine and feces (Litjens et al., 2004).

Effects of FAEs on the immune system are manifold. Using a comparable dosage (120 mg DMF plus other FAEs to a lesser extent) to DMF as designated for MS treatment, they have been shown to induce T cell apoptosis in healthy individuals (Litjens et al., 2004) and to reduce peripheral CD4+ and CD8+ lymphocytes in psoriasis patients (Hoxtermann et al., 1998).

Intracellular ATP levels of CD4+ cells — as a potential surrogate parameter for T cell function (Haghikia et al., 2011) — showed no differences in psoriasis patients with or without DMF treatment (Gambichler et al., 2012). This may be a first hint aiming rather at an immunomodulatory than immunosuppressive effect of FAEs.

This is further supported by experimental data that FAE can induce a Th2 cytokine shift with an interleukin (IL)-4 and IL-5 dominated cytokine response and reduced interferon-gamma production (Ockenfels et al., 1998; Zoghi et al., 2011). Effects on other immune cells and CNS cells have been described (Lin et al., 2011; Vandermeeren et al., 1997; Wierinckx et al., 2005). In addition to immunomodulatory properties, further mechanisms of action can thus be postulated.

Interactions with nuclear factor-kappa B (NF-κB) and nuclear (erythroid-derived2)-related factor (Nrf2) will be further elucidated in this context.

DMF inhibits the translocation of NF-κB and thus suppresses NF-κB-dependent transcription. This results in anti-inflammatory effects by reduction of pro-inflammatory cytokines, adhesion molecules and induction of apoptosis, but also in a regulation of cell survival by interfering with cellular redox-systems (Mrowietz and Asadullah, 2005; Stoof et al., 2001; Vandermeeren et al., 1997). Reduced NF-κB activation results in reduced activity of nitric oxide synthase 2 (NOS-2) and thus reduced nitrite accumulation, but increased mRNA levels of enzymes involved in glutathione synthesis (Lin et al., 2011). Anti-oxidative mechanisms and putative cytoprotective properties of DMF have therefore been further investigated. In this context, Nrf2 is of interest as it induces the transcription of several anti-oxidative genes. Among these genes are pathways that reduce oxidative stress and may thus preserve myelin integrity (Linker et al., 2011; Papadopoulou et al., 2010).

On a cellular level, the application of DMF (or MMF) leads to intranuclear translocation of Nrf2, and enhances Nrf2-dependent transcription and thus the expression of anti-oxidative enzymes in experimental models (Linker et al., 2011; Liu et al., 2007). This hypothesis was further supported by in vitro studies documenting prolonged survival of neurons and glial cells, an effect that was lost in Nrf2-deficient cells (Scannevin et al., 2012).

Experimental autoimmune encephalomyelitis (EAE) is a widely used murine model of MS. It can be induced by injection of myelin oligodendrocyte glycoprotein (MOG) (Gold et al., 2006). In this model, DMF treatment also augments Nrf2 levels in the CNS and results in an ameliorated disease course, especially in late stages of EAE (Linker et al., 2011).

These experimental data will have to be further confirmed by human data and long-term data, especially on disability progression in later stages of MS to prove significant neuroprotective effects in human disease.

Clinical trials and efficacy outcomes

DMF in enteric-coated capsules ("BG12") was investigated in a multicenter, randomized, double-blind phase-II trial with an initial placebo-controlled phase followed by an extension phase with different dose regimens (Kappos et al., 2008).

The trial investigated a once daily (120 mg) versus two different thrice daily dosages of FAE (3× 120 mg vs. 3× 240 mg). During the extension phase, the placebo group was switched to the high-dose thrice daily regimen.

After the double-blind study period of 24 weeks, a significant reduction of new gadolinium-enhancing MRI lesions, of new/enlarging T2-hyperintense and new T1-hypointense lesions was only shown comparing the high-dose group vs. placebo. These positive results were corroborated by post hoc and subgroup analyses (Kappos et al., 2012; MacManus et al., 2011). Interestingly, the evolution of T1-hypointense lesions from gadolinium-enhancing lesions seemed to be specifically suppressed by the high-dose regimen (Kappos et al., 2012). This may argue for reduced sustained tissue destruction and reflect putative neuroprotective mechanisms.

Following these promising data, two pivotal phase-III trials in RRMS (DEFINE, CONFIRM) were conducted (Table 1B) (Fox et al., 2012; Gold et al., 2012).

The randomized, double-blind DEFINE trial investigated twice and thrice daily DMF in a dosage of 240 mg vs. placebo with the primary endpoint of the proportion of relapse-free patients after 2 years (Gold et al., 2012). Secondary endpoints included further clinical measures

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