Journal of Neuroimmunology 231 (2011) 15–22

Contents lists available at ScienceDirect

Journal of Neuroimmunology

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

Review article

Emerging disease-modifying oral therapies for multiple sclerosis

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ARTICLE INFO

Keywords:
Multiple sclerosis (MS)
Fingolimod (FTY720)
Cladribine
Laquinimod (LAQ)
Dimethylfumarate (BG00012)
Teriflunomide

ABSTRACT

Although therapy for multiple sclerosis (MS) has changed substantially over the past few decades, introducing immunomodulatory drugs into everyday clinical practice, it is still not satisfactory enough in halting the disease progression and increasing disability. Moreover, its injection-based administration leads to suboptimal adherence, even further reducing the potential treatment benefits. Emerging disease-modifying oral agents for MS are therefore warranted. In this paper advances in the novel oral therapeutic approaches to MS treatment are reviewed.

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1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS), that is characterized by multiple areas of CNS white matter inflammation, demyelination, glial scarring (sclerosis), perivascular leukocyte infiltration, axonal damage and neuronal loss (Peterson and Fujinami, 2007;

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0165-5728/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jneuroim.2010.09.016

Rowland, 2005). Being the most common cause of neurological disability in young adults, it represents a prototypic autoimmune inflammatory disorder of the CNS (Kieseier et al., 2009). However, a clear, step-by-step pathomechanism underlying the disease has not yet been fully understood. The mode of action of currently approved disease-modifying drugs (DMDs) for MS is based on immunomodulation. They include recombinant interferons and glatiramer acetate as first-line treatment, with natalizumab and mitoxantrone as second-line therapies. Their efficacy is only partial, and since they are all administered parenterally, they are associated with patients' discomfort, local side effects (injection-site reactions), and therefore, poor adherence. Increasing knowledge about MS immunopathogenesis has given rise to a number of new potential therapeutic targets, which interact with the immunological system on several levels.

Emerging oral therapies for MS are an especially attractive alternative to current DMDs. As they do not rely on injections, they are convenient in use, hence the hope for a much better adherence. Several oral drugs for MS are under development, including fingolimod, oral cladribine, teriflunomide, oral fumarates and laquinimod. Differing in their mode of action (Fig. 1) and potential adverse events, they have been or are now evaluated in phase III clinical trials, which seem to indicate some promising results. The most important data concerning each drug's stage of development, primary outcome measures, dosing regimen and adverse effects are presented in Table 1. Their chemical structures are presented in Table 2.

In this review we are presenting the basic characteristics of the most promising oral agents for MS, together with the results obtained from clinical and preclinical trials. Hoping that the search for an orally available disease-modifying drug for MS will soon end up with a number of possible choices matched for individual patients, we cannot dispose of a dose of sceptisim, and thus the potential threats and pitfalls of emerging oral therapies will also be discussed.

2. Fingolimod (FTY720)

A structural analogue of sphingosine, fingolimod is derived from the fungus *Isaria sinclairii* and exerts unique immunoregulatory effects (Kieseier et al., 2009).

2.1. Mechanism of action and experimental animal models

Fingolimod is a non-selective sphingosine-1-phospate (S1P) receptor modulator that reversibly sequesters lymphocytes, mainly in the lymph nodes, reducing their recirculation to the CNS and, as a consequence, abrogating the neuroinflammatory process. Binding of fingolimod to S1P receptors induces internalization of these receptors and blocks lymphocyte egress from the secondary lymphoid structures. It depletes CD4+ cells more than CD8+ cells and does not affect innate immune cells, monocytes or NK cells. Due to its mechanism of action, FTY720 obviously causes lymphocytopenia, however, it does not result in immunosupression, since the activation of T-cells or memory cells responses are intact (Kieseier et al., 2009). Being of lipophilic nature, FTY720 easily crosses the blood-brain barrier (BBB) and interacts with S1P receptors within the CNS. Fingolimod is potentially neuroprotective, enhancing myelination and axonal protection in animal models (Rammohan and Shoemaker, 2010). It may also be considered as vasoprotective, increasing endothelial barrier integrity (Brinkmann et al., 2004).

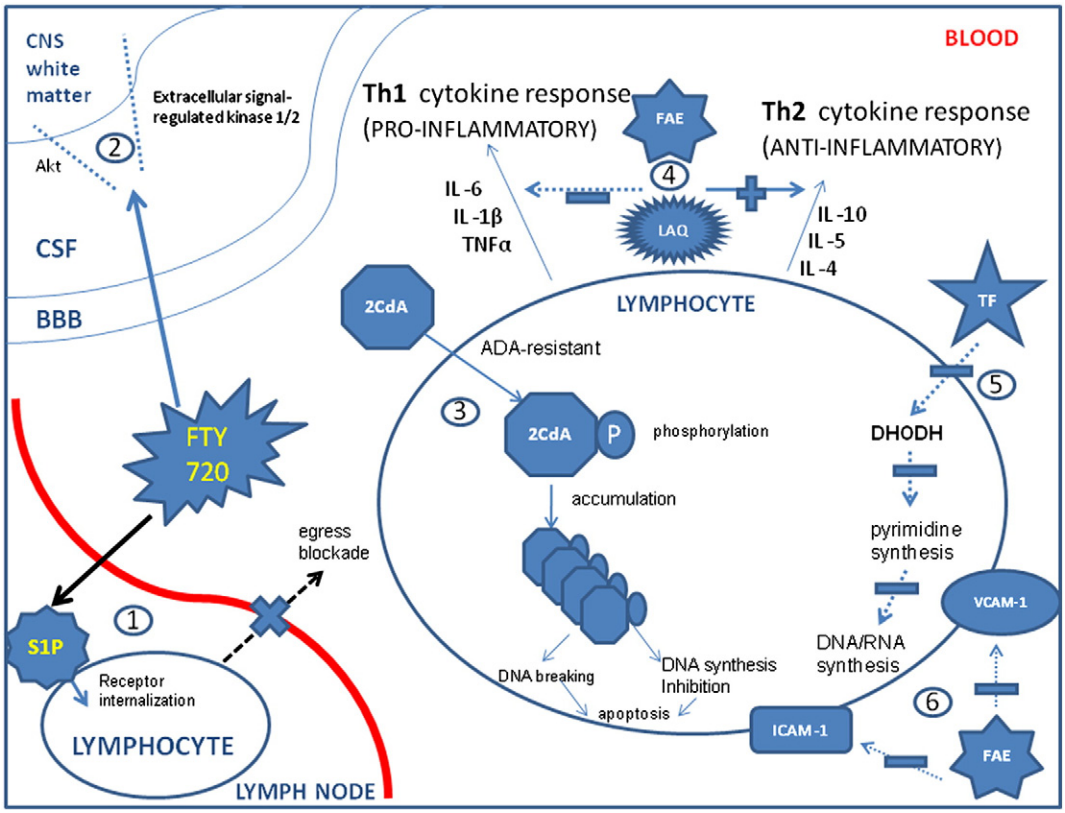

Fig. 1. Schematic presentation of the main mechanisms of action of different oral anti-MS agents.① Blockade of lymphocyte migration out of secondary lymphoid structures (FTY720).② Direct effect on oligodendrocytes – protection from apoptosis (FTY720).③ Accumulation of deoxynucleotides in lymphocytes – induction of apoptosis (2CdA).④ Induction of a shift from Th1 to Th2 cytokine response (FAE, LAQ).⑤ Lymphocyte supression by blocking pyrimidine synthesis (TF).⑥ Adhesive molecules downregulation leading to reduced migration across the BBB (FAE).FTY720 — fingolimod, FAE — fumarates, LAQ — laquinimod, 2CdA — 2-chlorodeoxyadenosine (cladribine), TF — teriflunomide, CNS — central nervous system, BBB — blood-brain barrier, CSF-cerebrospinal fluid, DHODH — dihydroorotate dehydrogenase, ADA — adenosine deaminase.

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