Mini Review Article

Fingolimod (FTY720) for Ischemic Stroke

Shahram Ghiyasvand, Sepideh Zununi Vahed, Mohammadreza Ardalan*

Kidney Research Center, Tabriz University of Medical Sciences, Tabriz Iran.

Abstract

Brain ischemic events abruptly start an expanding wave of cytokines release and oxidative stress within the brain tissue. This inflammatory storm alters the permeability of brain blood barrier (BBB), upregulates the endothelial cell adhesion molecules (ICAMs) and causing intense inflow of inflammatory cells toward the ischemic brain. This inflammatory phase further exacerbates the brain damage. In a second phase, after a few days, brain, via intense noradrenergic discharge targets the peripheral immune system and create general immunosuppression to protect itself from inflammation. Fingolimod (FTY720) a high-affinity agonist of sphingosine-1-phosphate (S1P) prevents S1P mediated lymphocytes migration from lymph node toward the systemic circulation and finally to the brain during the early phase of ischemic stroke.

Keywords: Fingolimod, FTY720, Ischemic Stroke

Introduction

Brain ischemic events immediately trigger a local inflammatory process. Subsequent microglial and astrocytes activation and cytokines secretion create an expanding wave of inflammation and oxidative stress within the brain tissue. Increased permeability of the brain blood barrier (BBB) and up regulation of endothelial cell adhesion molecules such as selectins and ICAM-1 cause an intense inflow of inflammatory cells; macrophages, neutrophils and lymphocytes toward the ischemic area. Danger-associated molecular patterns (DAMPs) including purinergic molecules and high mobility group box 1 (HMGB1) protein that are released from damaged neurons not only activate brain resident cells but also via activation of peripheral immune system lead to further damages (Figure 1).

The fast and intense migration of lymphocytes from the peripheral lymph organs toward the brain tissue intensifies the focal inflammatory responses. It exacerbates the ischemic-inflammatory process and worsens the clinical outcomes [1]. Cytotoxic T cells that are the major mediator of early phase does not need classical antigen-mediated activation. Accordingly, IL-17 secreting γδ T lymphocyte and natural killer (NK) cells are important contributors. They perform their destructive effect via interferon-γ and perforin release. Regulatory T cells (Treg) and B cells (Breg) damping the immune response. The later one even without entering the ischemic brain confer neuroprotection through an IL-10 secretion [2]. Inflammation is a key contributor in the pathophysiology of stroke, as its waves even reaches distant lymphoid organs to recruit more inflammatory cells toward the brain [3].

First phase: immune system attacks the brain

Fingolimod (FTY720), a high-affinity agonist of sphingosine-1-phosphate (S1P), binds to G protein coupled S1P receptors (S1P1, S1P3–5). It is the first oral immunomodulatory drug for multiple sclerosis (MS) that is approved by the FDA in 2010.

By its high affinity binding to S1P receptors, FTY720 prevents S1P-mediated lymphocytes migration from lymph node toward
FTY720 attaches to S1P receptors expressed on the membrane surfaces of cells including neurons, astrocytes, microglia, and endothelial cells and blocks the lympho-attractant capacity. Fingolimod is a promising neuroprotective drug against stroke [4]. The therapeutic effect of FTY720 on acute ischemic stroke was first described in experimental models of ischemic stroke [5,6]. Future clinical studies showed the clinical benefit of FTY720 treatment. The patients who received combined alteplase and oral fingolimod compared with alteplase arm exhibited lower circulating lymphocytes and significantly smaller lesion volumes [7]. Beneficial effect of FTY720 on neurological impairment of acute ischemic stroke and even on intracerebral hemorrhage has been shown by another studies [8,9] in a recent prospective randomized clinical trial FTY720 administration; 0.5 mg for three days expands the time-window of thrombolysis effectiveness in patients with ischemic stroke [10]. FTY720 was reported to be associated with cardiovascular side effects such as bradycardia and atrioventricular blockages during the early clinical trials for multiple sclerosis [11]. In clinical trials that used fingolimod for ischemic stroke there were no reported drug-related serious adverse effects [7,8].

**Second phase: brain induces peripheral immune suppression**

Within a few days after acute ischemic stroke occurs, both in experimental models and human studies lymphopenia develops and spleen size decreases. The volume of infarct is directly associated with the extent of lymphopenia and monocyte dysfunction [12]. The injured brain modulates peripheral immune system and its functional status from a competence to suppressive state after acute ischemic stroke [13].

Central nervous system can initiate a noradrenaline neuronal outflow which subsequently suppresses interferon gamma-secreting macrophages [14]. Brain originated noradrenaline releasing circuit also converts invariant natural killer T cells in liver to convert toward TH2 helper subtype and produce IL-10 cytokine. Physiologically this function could be reversed by propranolol administration [15].

**FTY720 effects beyond stroke**

Recent data from nephrology studies even move the field forward and another protective mechanisms has been elucidate. FTY720 administration attenuates AKI by direct effect on proximal tubule cells. Its mitochondrial preserving function is independent on its canonical lymphopenic effects [16]. Beneficial effects of FTY720 on prevention of ischemic brain tissue. This second wave of inflammatory infiltration intensely damages the ischemic area. Fingolimod (FTY720) blocks the lymphocytes exist and prevents the lymphocytes brain invasion during the early stages of ischemic stroke.
of lympho-monocyte infiltration, was observed during the late phase of renal IRI as it effectively reduces cell infiltrates within the first week after transplantation [17]. FTY720 stabilizes endothelial junctions and reduce vascular permeability, and in experimental ischemic injured kidney it has been proposed that FTY720 may not only induces T-cell depletion but also improves endothelial cell barrier function [18]. FTY720 even reached clinical trial for kidney transplantation, but it was not as successful as it was anticipated at the start [19]. This new area in different field of medicines shows how come it is important to move from scientific ideas toward clinical studies, although sometimes the results are not straightforward and clinical scientists should be aware about unforeseen events that may happen during long run trials.

Conflict of interest
None

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References