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Review article

Update on the cardiovascular profile of fingolimod in the therapy of relapsing-remitting multiple sclerosis (MS)

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ABSTRACT

Background: Fingolimod (FTY720) has been approved as the first oral representative of the class of sphingosine-1-phosphate (S1P) receptor modulators for the treatment of relapsing-remitting multiple sclerosis (MS). Besides inducing vaso-relaxation, fingolimod can also influence electrical conduction in the myocardium and vascular endothelium by having a transient negative chronotropic effect on the sinus node.
Methods: Cardiac safety and tolerability of fingolimod in the cardiac sense were reviewed by analysing the data collected from the FREEDOMS and TRANSFORMS studies –both relevant studies for marketing authorisation, from their extension studies, as well as the clinical data collected from a practice-related MS patient cohort with cardiovascular risk factors and corresponding co-medication (FIRST study).
Results: The safety analyses on file gave no indication of any increased cardiovascular risk. The 2–3 mmHg increase in blood pressure observed after the first dose of fingolimod has no therapeutic consequences. The first dose of 0.5 mg fingolimod resulted in an average decrease in heart rate of 7–8 beats/min. The onset of effect occurred approximately 1–2 h after the first dose and the nadir was reached after approximately 4–5 h. This negative chronotropic effect returned to normal after internalisation of the S1P1 receptors on maintenance therapy. There were no indications that patients with cardiac risk factors required closer observation beyond the monitoring recommended by the EMA following the first dose of fingolimod. Case study observations from the routine clinical setting show that patients accept this method of monitoring, which they assess as being a positive aspect of attentive medical care and concern.

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Fingolimod (FTY720) has been approved as the first oral representative of the group of sphingosine-1-phosphate (S1P) receptor modulators for treatment of relapsing-remitting multiple sclerosis (MS). As part of the clinical study more than 11,000 patients were treated, thus totalling an overall exposure period of approximately 19,000 patient-years. Besides its immunomodulatory action, fingolimod can affect angiogenesis, vasorelaxation, and the electrical conduction in both the myocardium and vascular endothelium.

The European Medicines Agency (EMA) has issued recommendations for cardiovascular monitoring after the first application and reached a positive evaluation of the risk-benefit profile for fingolimod.

Fingolimod is a structural analogue of sphingosine, a physiologically naturally-occurring lysophospholipid in the human body. After oral application phosphorylation by sphingosine kinases forms the biologically active substance (S) fingolimod phosphate (FP), which acts as agonist at four (S1P1R, S1P3R, S1P4R, S1P5R) out of five known S1P-receptors following antagonistic activity of sphingosine-1-phosphate (S1P). Fingolimod exerts its effects relevant to MS by inhibiting the function of S1P1 receptors to favour conserved cysteines (CC)-chemokine receptor 7 (CCR7)-mediated retention of lymphocytes in lymph and potentially by directly targeting S1P-receptors in the central nervous system nodes (Brinkmann, 2010; Chun and Brinkmann, 2011; Ocker et al., 2011). Sphingosine-1-phosphate (S1P) belongs to the family of bioactive lysophospholipids which as pleiotropic mediators are involved in many cell functions, such as proliferation, cytoskeletal organisation, migration and morphogenesis. S1P binds to five transmembrane receptors from the G-protein-coupled receptors (GPCR) family: S1P1 to S1P5. S1P3 receptors are common and are expressed in various tissues, e.g. neural cells, endothelial cells, atrial myocytes, smooth muscle cells. S1P4 receptors are present in lymphoid and haematopoietic tissues, while S1P5 receptors are located especially in the central nervous system (CNS), here mainly in the oligodendrocytes.

The signal transduction of S1P1 is mainly conducted by $G_{i/o}$ class G proteins, while S1P2, S1P3 and S1P4 develop their effect via G_i, G_q, $G_{12/13}$, and S1P5 via G_i and $G_{12/13}$ (Brinkmann, 2007; Koyrakh et al., 2005; Sanna et al., 2004; Herr and Chun, 2007; Meyer zu Heringsdorf and Jakobs, 2007; Chun and Hartung, 2010). This results in the activation of various intracellular signalling cascades; their mechanisms of action are not yet fully clarified. G_i impedes the cyclic adenosine monophosphate (cAMP)-dependent upregulation of the calcium (Ca^{2+}) influx through the calcium channel by inhibiting adenylate cyclase. G_q increases the intracellular Ca^{2+} concentration, for example in smooth muscle cells. The GIRK channels (G protein-coupled inwardly-rectifying potassium ion $\{K\}_{channels}$) in the sinoatrial (SA) and atrioventricular (AV) nodes and in the atrial myocytes are important direct targets of $Gi_{/o}$(Bünemann et al., 1995; Brinkmann, 2009) (Table 1).

1. Fingolimod's mechanism of action

Fingolimod is principally phosphorylated by sphingosine kinase-2 (SphK2) to form fingolimod phosphate (FP) and, like S1P, is discharged from the cells by active transport mechanisms. Fingolimod, as the first molecule to be used therapeutically, targets the sphingosine phosphate receptor group. Following oral administration, fingolimod is phosphorylated by SphK2 to form the active substance (S) fingolimod-phosphate (FP), and binds itself with low affinity to S1P1R, S1P4R, S1P5R as well as to S1P3R (Maceyka et al., 2012). Fingolimod acts as a functional antagonist of the S1P receptors. The drug binds to the receptor, thereby triggering both internalisation and degradation of the receptor. Induced by the internalisation of the S1P1 receptor, its mechanism of action is primarily based on the reduction of the number of MS-relevant lymphocyte populations in the periphery - $CCR7^+$ naive T-cells (Tn) and autoreactive pathogenic central memory T cells (TCM). The emigration of the lymphocyte populations which is important for defending against infection - $CCR7^-$ effector memory T cells (TEM) – is not impaired by fingolimod (Brinkmann et al., 2010; Mehling et al., 2008; Metzler et al., 2008).

1.1. Approval status and clinical observations

Fingolimod is licensed as a first-line treatment for relapsing remitting multiple sclerosis, the most common form of the disease, in the USA, Canada, Australia, New Zealand, Switzerland and Russia. In Australia, the license also pertains to patients with secondary progressive MS (SPMS) with residual inflammatory activity (Broadley et al., 2014; Freedman et al., 2013).

According to the latest extension of indication Fingolimod is approved by the European Medicines Agency (EMA) in the European Union (EU) for

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease-modifying therapy (EU Community, 2016; Scolding et al., 2015).

or

- Based on the results of a recently performed MRI, patients with rapidly progressing, severe relapsing-remitting multiple sclerosis. This means two or more attacks with debility progression