Multiple sclerosis rebound upon fingolimod discontinuation: evidence and mechanisms involved

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Lymphocyte egress from lymphoid organs is driven by sphingosine 1-phosphate (S1P) gradient, indeed upon interaction between S1P1 receptor and S1P, immune cells are enabled to gain the blood stream. Fingolimod has been recently approved for treatment of relapsing-remitting MS thanks to its ability to mediate S1PRs internalization and degradation thereby trapping lymphocytes in lymphoid organs. Although treatment is supposed to be chronic, very recent contributions showed dramatic worsening in MS patients interrupting fingolimod therapy because of different reasons. To better understand molecular mechanism underlining disease worsening after drug withdrawal, we took advantage of both in vivo and in vitro models of fingolimod suspension. As for in vivo, using a model of relapsing-remitting EAE, we found that SJL mice undergo severe disease rebound few days after fingolimod suspension. Furthermore when we evaluated the effect of fingolimod withdrawal in vitro, on cultured mouse lymphocytes, we found that upon drug suspension, S1P1 levels (both transcript and protein) significantly increased. Interestingly the increase in S1P1 expression leads to higher Akt phosphorylation which suppresses the development and function of T regulatory cells (Treg). In line with this we found a decreased Treg number in mice treated with fingolimod after drug suspension. Taken together these findings indicate that upon fingolimod withdrawal the higher expression of S1P1 on lymphocyte may lead to decreased number of Treg and to a massive exit of immune cells from lymph nodes thereby driving disease rebound.