A New Therapeutic approach for Autoimmune Diseases by The Sphingosine 1-Phosphate Receptor Modulator, FTY720

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FTY720 (Fingolimod) is the first of a new immunomodulator class: sphingosine 1-phosphate (S1P) receptor modulator. We isolated an immunosuppressive natural product, myrocin from the culture broth of *Isaria sinclairii*, a kind of vegetative wasp. The chemical modification of myriocin yielded a new compound, FTY720, which has more potent immunosuppressive activity and less toxicity than myriocin. FTY720 has shown to be highly effective in experimental allograft models and autoimmune disease models such as autoimmune encephalomyelitis and collagen-induced arthritis. A most striking feature of FTY720 is the induction of a marked decrease in peripheral blood lymphocytes at doses that show immunosuppressive activity in these models. FTY720 is rapidly converted to FTY720-phosphate (FTY720-P) by sphingosine kinase. FTY720-P acts as a potent agonist at S1P receptor type 1 ($S1P_1$), internalizes $S1P_1$ on lymphocytes, and inhibits the migration of lymphocytes toward S1P. Thus it is highly likely that the reduction of peripheral blood lymphocytes by FTY720 is due to the inhibition of S1P/$S1P_1$-dependent lymphocyte egress from secondary lymphoid tissues and thymus. Recently, it has been reported that FTY720 exerts considerable therapeutic effects in a placebo-controlled clinical trail involving patients with relapsing multiple sclerosis. Patients who received FTY720 orally had a significant reduction in the clinical disease activity, the number of CNS lesions, and the relapse rates. Since FTY720 possesses a new mechanism of action that has not been observed with other immunosuppressive agents, it is presumed that FTY720 provides a new therapeutic approach for autoimmune diseases including multiple sclerosis and rheumatoid arthritis.