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Reduced fingolimod dosage treatment for patients with multiple sclerosis and lymphopenia or neutropenia

Fingolimod has been approved as the first oral treatment for relapsing–remitting multiple sclerosis (RRMS). In a Japanese clinical trial,[1] 8.9% of patients treated with 0.5mg of fingolimod showed lymphocyte counts of < 200 × 10^6/l and a reduction of the mean absolute neutrophil count of 14% and 25% from baseline at day 15 and month 6, respectively.

The maximum fingolimod concentration increased and nadir lymphocyte count decreased with dose after a single oral dose of fingolimod.[2] Steady-state plasma concentrations were attained 1–2 months after treatment initiation.[3] The steady-state plasma maximum drug concentrations were calculated from the maximum plasma concentration (C_{max}) and elimination half-life ($T_{1/2}$) of fingolimod. Steady-state C_{max} levels correlated with total doses for six contiguous days (dosing ranged from daily to every three days) (data not shown).

Patient 1: a 71-year-old woman with disease duration of 12 years. Two weeks after starting daily fingolimod treatment (0.5 mg/day: 3.0 mg/6 days) her lymphocyte counts decreased from 800 to 176 × 10^6/l. Lymphocytes increased to 300 × 10^6/l after changing administration from daily to every other day (0.5 mg e.o.d.: 1.5 mg/6 days: three weeks after initiation).

Patient 2: a 28-year-old woman with disease duration of one year and seven months. Five weeks after initiation, her lymphocyte count decreased (from 1292 × 10^6/l to 244 × 10^6/l) and gradually increased to 474 × 10^6/l after changing from daily (0.5 mg/day: 3 mg/6 days) to 5 times/6 days (0.5 mg/day: 2.5 mg/6 days) 15 weeks after initiation.

Patient 3: a 35-year-old woman with disease duration of 14 years. Her neutrophil count decreased from 2457 to 1336 × 10^6/l (38% reduction) seven weeks after initiation. Neutrophils increased to 1985 × 10^6/l after changing to 4 times/6 days (0.5 mg/day: 2.0 mg/6 days).

None of the three patients showed any clinical relapses in the 34–38 weeks from initiation.

Previous clinical trials of fingolimod have not shown that any patients with lymphopenia or neutropenia had to discontinue the study drug; however, we administered fingolimod to patients with small body habitus who may have shown higher drug blood concentration after phosphorylation. The body surface area (BSA) of our patients was 1.46, 1.55 and 1.45 m^2. Plasma concentration should be considered when treating women with small BSA. In an earlier, ethnic based study, no differences in blood concentration after single-dose administration were found between Caucasian and Japanese individuals, but the authors did not discuss BSA.[4] We should consider alternative treatment schedules that may include drug holidays within a weekly dosing schedule if patients show a rapidly decreasing lymphocyte count 2–4 weeks after initiation. The mechanisms of neutrophil reduction are not known, but there was no relationship between lymphocyte and neutrophil counts for these three patients.

We suggest that the lymphocyte count may correlate with the dosage of fingolimod (cumulative dose over several weeks) and that the lymphocyte can be controlled satisfactorily by administering the same 0.5 mg tablet at varying intervals.

Conflict of interest

The authors declare that there are no conflicts of interest.

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