**Lymphocyte counts and infection rates: long-term fingolimod treatment in primary progressive MS**

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**Table e-1** Incidences of all infections, respiratory tract infections, and herpes infections in patients with a low white blood cell count, a low absolute neutrophil count, and both a low absolute lymphocyte count and a low white blood cell count at any visit

|  |  |  |  |
| --- | --- | --- | --- |
|  | **WBCC ≤ 2 × 109/L** | **ANC ≤ 1 × 109/L** | **WBCC ≤ 2 × 109/Land ALC < 0.2 × 109/L** |
|  | **Fingolimod 0.5 mg/day(n = 11)** | **Fingolimod 1.25 mg/day(n = 11)** | **Fingolimod 0.5 mg/day(n = 2)** | **Fingolimod 1.25 mg/day(n = 2)** | **Fingolimod 0.5 mg/day(n = 4)** | **Fingolimod 1.25 mg/day(n = 4)** |
| All infections | 11 (100.0)[49.9; 178.9] | 7 (91.0)[36.6; 187.5] | 2 (220.0)[26.7; 794.8] | 2 (310.9)[37.7; 1123.0] | 4 (178.2)[48.6; 456.2] | 2 (51.7)[6.3; 186.8] |
| Upper respiratory tract infection | 4 (14.5)[4.0; 37.2] | 1 (10.2)[0.3; 56.9] | 1 (22.2)[0.6; 123.9] | 0 | 3 (62.1)[12.8; 181.4] | 0 |
| Viral upper respiratory tract infection | 4 (12.0)[3.3; 30.7] | 1 (9.4)[0.2; 52.5] | 0 | 0 | 1 (7.7)[0.2; 42.9] | 1 (25.3)[0.6; 141.2] |
| Oral herpes infection | 2 (6.2)[0.8; 22.3] | 0 | 1 (23.1)[0.6; 128.9] | 0 | 1 (8.8)[0.2; 49.2] | 0 |

Data are reported as numbers (incidences per 100 patient-years) [95% CI].

Abbreviations: ALC = absolute lymphocyte count; ANC = absolute neutrophil count; WBCC = white blood cell count.

**Table e-2** Incidences of all infections, respiratory tract infections, and herpes infections per 100 patient-years among subjects initially receiving fingolimod 1.25 mg who switched to fingolimod 0.5 mg based on nadir absolute lymphocyte count

|  |  |
| --- | --- |
|  | **Nadir absolute lymphocyte count (fingolimod 1.25 mg/0.5 mg)** |
|  | **< 0.2 ×109/L(n = 25)** | **0.2–0.3 ×109/L(n = 52)** | **0.3–0.4 ×109/L(n = 23)** | **0.4–0.5 ×109/L(n = 15)** | **0.5–0.7 ×109/L(n = 3)** | **> 0.7 ×109/L(n = 3)** |
| All infections | 20 (52.7)[32.2; 81.3] | 36 (43.7)[30.6; 60.6] | 20 (84.2)[51.4; 130.1] | 11 (35.3)[17.6; 63.2] | 3 (42.9)[8.8; 125.2] | 2 (40.9)[5.0; 147.8] |
| Upper respiratory tract infection | 4 (4.9)[1.3; 12.5] | 9 (5.7)[2.6; 10.7] | 6 (8.4)[3.1; 18.3] | 1 (1.7)[0.0; 9.4] | 0 | 0 |
| Viral upper respiratory tract infection | 11 (17.6)[8.8; 31.5] | 13 (8.1)[4.3; 13.8] | 9 (14.6)[6.7; 27.8] | 1 (1.7)[0.0;6.5] | 1 (8.4)[0.2; 46.7] | 0 |
| Oral herpes infection | 0 | 1 (0.5)[0.0; 3.1] | 2 (2.3)[0.3, 8.5 | 1 (1.7)[0.0, 9.7] | 0 | 0 |

Data are reported as numbers (incidences per 100 patient-years) [95% CI].

**Table e-3** Incidences of all infections, respiratory tract infections, and herpes infections per 100 patient-years among subjects initially receiving fingolimod 1.25 mg who switched to fingolimod 0.5 mg based on mean absolute lymphocyte count

|  |  |
| --- | --- |
|  | **Mean absolute lymphocyte count (fingolimod 1.25 mg/0.5 mg)** |
|  | **< 0.2 ×109/L(n = 0)** | **0.2–0.3 ×109/L(n = 17)** | **0.3–0.4 ×109/L(n = 33)** | **0.4–0.5 ×109/L(n = 29)** | **0.5–0.7 ×109/L(n = 29)** | **> 0.7 ×109/L(n = 13)** |
| All infections | 0 | 15 (74.6)[41.8; 123.11] | 20 (32.4)[19.8; 50.1] | 25 (87.8)[56.8; 129.6] | 23 (49.8)[31.6; 74.8] | 9 (29.4)[13.4; 55.8] |
| Upper respiratory tract infection | 0 | 1 (1.8)[0.1; 10.0] | 5 (4.9)[1.6; 11.3] | 10 (13.2)[6.3; 24.3] | 4 (3.6)[1.0; 9.4] | 0 |
| Viral upper respiratory tract infection | 0 | 7 (18.3)[7.4;37.8] | 9 (9.8)[45; 18.6] | 9 (10.3)[4.7; 19.6] | 9 (9.0)[4.1; 17.2] | 1 (2.0)[0.1; 11.1] |
| Oral herpes infection | 0 | 0 | 1 (0.9)[0.0, 5.1] | 2 (1.9)[0.2, 6.9] | 1 (0.8)0.0, 4.7] | 0 |

Data are reported as numbers (incidences per 100 patient-years) [95% CI].

**Table e-4** Correlation of mean absolute lymphocyte count with occurrence of skin malignancies

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Mean lymphocyte count (fingolimod 0.5 mg)** | **All fingolimod 0.5 mg** | **Placebo** |
|  | **< 0.2 ×109/L(n = 2)** | **0.2–0.3 ×109/L(n = 44)** | **0.3–0.4 ×109/L(n = 79)** | **0.4–0.5 ×109/L(n = 58)** | **0.5–0.7 ×109/L(n = 89)** | **> 0.7 ×109/L(n = 64)** | **(n = 336)** | **(n = 487)** |
| Basal cell carcinoma | 0 | 1 (2.3) | 3 (3.8) | 3 (5.2) | 3 (3.4) | 4 (6.3) | 14 (4.2) | 9 (1.8) |
| Malignant melanoma | 0 | 0 | 0 | 0 | 1 (1.1) | 0 | 1 (0.3) | 0 |
| Squamous cell carcinoma of the skin | 0 | 1 (2.3) | 0 | 0 | 4 (4.5) | 1 (1.6) | 6 (1.8) | 1 (0.2) |
| Any of the above | 0 | 2 (4.5) | 3 (3.8) | 3 (5.2) | 6 (6.7) | 4 (6.3) | 18 (5.4) | 10 (2.1) |

Data are reported as numbers (%).

**Table e-5** Correlation of nadir absolute lymphocyte count with occurrence of skin malignancies

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Nadir absolute lymphocyte count (fingolimod 0.5 mg)** | **All fingolimod 0.5 mg** | **Placebo** |
|  | **< 0.2 ×109/L(n = 59)** | **0.2–0.3 ×109/L(n = 108)** | **0.3–0.4 ×109/L(n = 65)** | **0.4–0.5 ×109/L(n = 55)** | **0.5–0.7 ×109/L(n = 40)** | **> 0.7 ×109/L(n = 9)** | **(n = 336)** | **(n = 487)** |
| Basal cell carcinoma | 1 (1.7) | 6 (5.6) | 1 (1.5) | 2 (3.6) | 4 (10.0) | 0 | 14 (4.2) | 9 (1.8) |
| Malignant melanoma | 0 | 0 | 0 | 1 (1.8) | 0 | 0 | 1 (0.3) | 0 |
| Squamous cell carcinoma of the skin | 1 (1.7) | 3 (2.8) | 0 | 1 (1.8) | 1 (2.5) | 0 | 6 (1.8) | 1 (0.2) |
| Any of the above | 2 (3.4) | 8 (7.4) | 1 (1.5) | 3. (5.5) | 4 (10.0) | 0 | 18 (5.4) | 10 (2.1) |

Data are reported as numbers (%).

**Figure e-1** Recovery of absolute lymphocyte count following fingolimod treatment discontinuation (overall fingolimod 0.5 mg/day group)



Non-uniform time axis; +, mean; middle bar, median; box, Q1−Q3 interval; whisker, range.

Abbreviation: ALC = absolute lymphocyte count.

**Figure e-2** Incidences of all infections, respiratory tract infections, and herpes infections in patients receiving fingolimod 1.25 mg/day

Incidences of all infections, respiratory tract infections, and herpes infections in patients receiving fingolimod 1.25 mg/day stratified by (A) nadir ALC and (B) mean ALC (left-hand side). Right-hand side shows the overall incidences in patients receiving fingolimod 1.25 mg/day, fingolimod 0.5 mg/day or placebo.

aIncludes viral and other upper and/or lower respiratory tract infections. bIncludes oral herpes, herpes simplex, herpes zoster, herpes zoster meningomyelitis, genital herpes, neurological herpes, ophthalmic herpes simplex, and ophthalmic herpes zoster.

Error bars represent 95% CI.
Abbreviation: ALC = absolute lymphocyte count.

**Figure e-3** Cumulative development of infectious complications over time (Kaplan−Meier analysis)



Data are shown as cumulative failure rate for number cumulative events/number of patients at risk in the fingolimod 0.5 mg and placebo groups