Fingolimod: Viruses and Vaccines

State of the Art
2014
Luzern

Tobias Derfuss
Neurologische Klinik und Poliklinik
Universitätsspital Basel
Fingolimod prevents lymphocyte egress from lymph nodes.

Fingolimod causes:
1. Internalisation of the S1P₁ receptor
2. Inhibition of lymphocyte egress along the S1P gradient

CNS, central nervous system; S1P, sphingosine 1-phosphate


Fingolimod induces reversible retention of circulating lymphocytes in lymph nodes, reducing peripheral lymphocyte counts and their recirculation to the CNS.
Fingolimod acts only on circulating T cells

About 70% of lymphocytes are retained

Circulating lymphocytes:
- Naive T cells
- Central memory T cells (incl. Th17)
- B cells

Fingolimod

Blood: only <2% of total lymphocytes (10 x 10⁹)

Tissues
- Lymph nodes (190 x 10⁹)
- T cells homed in tissues: Effector memory lymphocytes

Lymph nodes (190 x 10⁹)

Fingolimod leads to reversible redistribution of lymphocytes, with no lymphocytotoxicity

**Rapid**
Lymphocytes are retained in the lymph nodes
Lymphocyte count reduced within 4–6 hours (max after 1–2 weeks)

**Reversible**
Retention of lymphocytes in lymph nodes
Lymphocytotoxicity is avoided
Lymphocyte function is maintained
Recovery back to normal in 1-2 months
Effects of Fingolimod treatment on T-cells

- Fingolimod reduces T-cells in peripheral blood
- mainly naive and central memory T-cells are reduced

Ricklin et al., Neurology, 2013
Distribution of virus-specific CD8+ memory T cells during infection:
Most virus-specific T cells are found within the TEM subset.

Adapted from Appay V et al. Cytometry Part A, 2008; 73A:975.
Fingolimod preserves key immune functions: similar infection rate to placebo

Table 2. Incidence of infections in the pooled treatment population from the integrated clinical trial population

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Fingolimod 0.5 mg (n=1212)</th>
<th>Fingolimod 1.25 mg (n=1313)</th>
<th>Placebo (n=866)</th>
<th>Interferon beta-1a IM (n=431)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one infection AE*</td>
<td>789 (65.1)</td>
<td>830 (63.2)</td>
<td>588 (67.9)</td>
<td>220 (51.0)</td>
</tr>
<tr>
<td>Any serious infection</td>
<td>19 (1.6)</td>
<td>26 (2.0)</td>
<td>12 (1.4)</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>Infection AEs per 100 patient-years</td>
<td>126.3</td>
<td>131.6</td>
<td>129.8</td>
<td>107.7</td>
</tr>
<tr>
<td>LRTI per 100 patient-years</td>
<td>0.8</td>
<td>1.0</td>
<td>1.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Bronchitis per 100 patient-years</td>
<td>5.8</td>
<td>7.3</td>
<td>4.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Pneumonia per 100 patient-years</td>
<td>0.5</td>
<td>0.9</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Any herpes infection per 100 patient-years</td>
<td>6.3</td>
<td>5.9</td>
<td>5.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Herpes zoster per 100 patient-years</td>
<td>1.0</td>
<td>1.2</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

The incidence of infections per 100 patient-years was calculated as the number of infections divided by the patient-years in treatment group, multiplied by 100. The patient-year denominator was defined as the sum of the number of days on study drug for all patients in each treatment group divided by 365.25.

*Treatment time in clinical trials: placebo, 6 (phase 2 study) and 24 months (FREEDOMS and FREEDOMS II); fingolimod, 12 (TRANSFORMS) and 24 months (FREEDOMS and FREEDOMS II); interferon beta-1a IM, 12 months (TRANSFORMS).

LRTI, lower respiratory tract infection

Methods: Safety data are described for a treatment population pooled from the following clinical trials: fingolimod 0.5 mg and 1.25 mg from phase 3 studies (FREEDOMS and FREEDOMS II [both 24 months vs placebo] and TRANSFORMS [12 months vs intramuscular (IM) interferon beta-1a]), and for fingolimod 5.0 mg and 1.25 mg from the phase 2, 6-month study.

The incidence of infections per 100 patient-years was calculated as the number of infections divided by the patient-years in treatment group, multiplied by 100. The patient-year denominator was defined as the sum of the number of days on study drug for all patients in each treatment group divided by 365.25.

+ The approved dose of fingolimod is 0.5mg; LRTI, lower respiratory tract infection

* Cohen et al, Multiple Sclerosis Journal 2012; 18: (S4) 454; Presented at ECTRIMS 2012
No clear relationship between lymphocyte counts and infection

Pooled analyses: D2201 and D2201E1, FREEDOMS (D2301) & D2301E1, TRANSFORMS (D2302) and D2302E1

Francis et al., Lymphocytes and fingolimod – temporal pattern and relationship with infections; Poster P442, ECTRIMS 2010, Francis et al., 2013, Mult Scler
Incidence of infections in FREEDOMS in fingolimod-treated patients categorized by nadir lymphocyte count

<table>
<thead>
<tr>
<th>Patients with infections, n (%)</th>
<th>Nadir lymphocyte counts in all fingolimod groups combined</th>
<th>Placebo (n = 418)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.2 ( \times 10^9 )/L n = 206</td>
<td>0.2–0.4 ( \times 10^9 )/L n = 475</td>
</tr>
<tr>
<td>Any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with infections, n (%)</td>
<td>156 (75.7)</td>
<td>344 (72.4)</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>114 (55.3)</td>
<td>254 (53.5)</td>
</tr>
<tr>
<td>Lower respiratory tract</td>
<td>25 (12.1)</td>
<td>53 (11.2)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>20 (9.7)</td>
<td>47 (9.9)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>11 (5.3)</td>
<td>31 (6.5)</td>
</tr>
<tr>
<td>Not classified</td>
<td>11 (5.3)</td>
<td>22 (4.6)</td>
</tr>
<tr>
<td>Dental and oral soft tissue</td>
<td>8 (3.9)</td>
<td>17 (3.6)</td>
</tr>
<tr>
<td>Ear</td>
<td>5 (2.4)</td>
<td>15 (3.2)</td>
</tr>
<tr>
<td>Female reproductive tract</td>
<td>4 (1.9)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Skin</td>
<td>4 (1.9)</td>
<td>15 (3.2)</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>1 (0.5)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Eye and eyelid</td>
<td>1 (0.5)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Breast</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Muscle and soft tissue</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Infection types are sorted in descending frequency for the group with nadir lymphocyte count <0.2\( \times 10^9 \)/L. Patients with multiple events can be included in more than one row.

P983 Cohen JA et al. ECTRIMS, 10–13 October 2012, Lyon, France (data on file), Francis et al., 2013, Mult Scler
Real-life data from USA and Canada (EPOC study): no relationship between peripheral lymphocyte counts and infection incidence

LaGanke et al., Poster 545 presented at ENS 2013
Incidence of infections with long-term fingolimod treatment

**FREEDOMS: 2-years**
- Placebo (n = 418)
- Fingolimod 0.5 mg (n = 425)

**FREEDOMS extension: 4-years**
- Placebo (Month 0–24) to fingolimod 0.5 mg (n = 155)
- Continuous fingolimod 0.5 mg (n = 331)

**Pooled Phase II and III: 6-months, 1- and 2-years (core studies only)**
- Fingolimod 0.5 mg (n = 1212)

---

At least one infection
- Placebo: 72.0%
- Fingolimod: 71.5%
- Placebo: 70.3%
- Fingolimod: 72.5%
- Placebo: 65.1%

Any serious infection
- Placebo: 1.9
- Fingolimod: 1.6
- Placebo: 0.6
- Fingolimod: 2.4
- Placebo: 1.6
- Fingolimod: 1.6

Herpes viral infection
- Placebo: 7.9
- Fingolimod: 8.7
- Placebo: 9.0
- Fingolimod: 12.1
- Placebo: 6.3
- Fingolimod: 6.3

---

**References**
FREEDOMS 4 years: infections during core phase and extension phase (safety population)

All patients receiving fingolimod 1.25 mg were switched to fingolimod 0.5 mg after the fingolimod 1.25 mg dose was discontinued from all multiple sclerosis clinical studies. Core safety data taken from Kappos L et al. N Engl J Med 2010;362:387-401. P523.Phase 3 FREEDOMS study extension: Long-term safety of fingolimod (FTY720) in relapsing–remitting multiple sclerosis. ECTRIMS, Lyon, France 2012.

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Continuous-fingolimod 0.5 mg (n=331)</th>
<th>Continuous-fingolimod 1.25 mg (n=289)</th>
<th>Placebo-Fingolimod 0.5 mg (n=155)</th>
<th>Placebo-Fingolimod 1.25 mg (n=145)</th>
<th>Fingolimod 0.5 mg (n=425)</th>
<th>Fingolimod 1.25 mg (n=429)</th>
<th>Placebo (n=418)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>240 (72.5)</td>
<td>204 (70.6)</td>
<td>109 (70.3)</td>
<td>100 (69.0)</td>
<td>304 (71.5)</td>
<td>294 (68.5)</td>
<td>301 (72.0)</td>
</tr>
<tr>
<td>Influenza</td>
<td>33 (10.0)</td>
<td>30 (10.4)</td>
<td>12 (7.7)</td>
<td>9 (6.2)</td>
<td>55 (12.9)</td>
<td>40 (9.3)</td>
<td>41 (9.8)</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
<td>3 (1.9)</td>
<td>2 (1.4)</td>
<td>4 (0.9)</td>
<td>3 (0.7)</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>21 (6.3)</td>
<td>19 (6.6)</td>
<td>11 (7.1)</td>
<td>11 (7.6)</td>
<td>34 (8.0)</td>
<td>39 (9.1)</td>
<td>15 (3.6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
<td>3 (1.9)</td>
<td>2 (1.4)</td>
<td>2 (0.5)</td>
<td>7 (1.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>7 (2.1)</td>
<td>2 (0.7)</td>
<td>0</td>
<td>5 (3.4)</td>
<td>7 (1.6)</td>
<td>4 (0.9)</td>
<td>9 (2.2)</td>
</tr>
</tbody>
</table>
TRANSFORMS 4.5 year: infections reported in extension phase

<table>
<thead>
<tr>
<th>Preferred name</th>
<th>Switch group</th>
<th>Continuous group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interferon-fingolimod 0.5 mg (N=167) n (%)</td>
<td>Interferon-fingolimod 1.25 mg (N=174) n (%)</td>
</tr>
<tr>
<td>Overall AEs</td>
<td>154 (92.2)</td>
<td>168 (96.6)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>51 (30.5)</td>
<td>53 (30.5)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>21 (12.6)</td>
<td>28 (16.1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>18 (10.8)</td>
<td>10 (5.7)</td>
</tr>
<tr>
<td>Influenza</td>
<td>17 (10.2)</td>
<td>17 (9.8)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>8 (4.8)</td>
<td>6 (3.4)</td>
</tr>
<tr>
<td>LRT infections</td>
<td>4 (2.4)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

P517 Montalban et al. Long-term comparison of fingolimod with interferon beta-1a: results of 4.5-year follow-up from the extension phase III TRANSFORMS study. ECTRIMS, Lyon, France, 2012

Phase II trial after 7-8 years: infections reported in extension phase (Safety population, close-out analysis)

<table>
<thead>
<tr>
<th>Adverse Event, AEs, n (%)</th>
<th>Placebo/ Fingolimod (N=93)</th>
<th>Fingolimod 1.25 mg (N=94)</th>
<th>Fingolimod 5.0 mg (N=94)</th>
<th>All N=281</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any infection</td>
<td>70 (75.3)</td>
<td>72 (76.6)</td>
<td>77 (81.9)</td>
<td>219 (77.9)</td>
</tr>
<tr>
<td>Any severe infection</td>
<td>3 (3.2)</td>
<td>4 (4.3)</td>
<td>5 (5.3)</td>
<td>12 (4.3)</td>
</tr>
<tr>
<td>Any serious infection</td>
<td>4 (4.3)</td>
<td>0</td>
<td>2 (2.1)</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>34 (36.6)</td>
<td>39 (41.5)</td>
<td>42 (44.7)</td>
<td>115 (40.9)</td>
</tr>
<tr>
<td>Influenza</td>
<td>16 (17.2)</td>
<td>23 (24.5)</td>
<td>22 (23.4)</td>
<td>61 (21.7)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>19 (20.4)</td>
<td>19 (20.2)</td>
<td>18 (19.1)</td>
<td>56 (19.9)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>9 (9.7)</td>
<td>17 (18.1)</td>
<td>12 (12.8)</td>
<td>38 (13.5)</td>
</tr>
</tbody>
</table>

N: number of patients in the ITT population; n: number of patients in the category. Placebo/Fingolimod: Placebo (core only) followed by fingolimod 5.0 or 1.25 mg followed by fingolimod 1.25 mg, and fingolimod 0.5 mg; Fingolimod 1.25 mg: Fingolimod 1.25 mg followed by fingolimod 0.5 mg; Fingolimod 5.0 mg: Fingolimod 5.0 mg followed by fingolimod 1.25 mg and fingolimod 0.5 mg.

PO1.129, Long-Term (7-Year) Data from a Phase 2 Extension Study of Fingolimod in Relapsing Multiple Sclerosis. AAN 2012, New Orleans, LA, USA, 21-28 April 2012.
Focus on herpesviral infections

- generalized fatal VZV infection in VZV naive patient during phase III trial (death due to liver failure)
- herpes simplex encephalitis
- generalized fatal VZV infection in the post-marketing setting; patient was positive for VZV-antibodies
- in all cases concomitant steroid treatment
VZV specific IFNg producing cells are reduced during Fingolimod treatment

Ricklin et al., Neurology, 2013
Number of VZV specific proliferating T-cells is reduced during Fingolimod treatment
Viral reactivation in saliva

Fingolimod treated patients
- no reactivation: 28
- EBV reactivation: 4
- VZV reactivation: 3

Healthy controls
- no reactivation: 51
- EBV reactivation: 2
- VZV reactivation:

Ricklin et al., Neurology, 2013
Precautions regarding VZV infections

• vaccinate VZV antibody negative patients before fingolimod start

• generalized VZV infection might develop with atypical symptoms; in case of suspicious symptoms (unusual for MS relapse) contact infectiologist

• avoid steroid tapering after relapse treatment

• consider aciclovir prophylaxis during steroid pulse therapy
Focus on PML during fingolimod treatment

- PML might occur during fingolimod treatment due to carry-over from previous natalizumab therapy (so far three cases)
  - perform baseline MRI to exclude PML suspicious lesions
  - exclude PML by JCV-PCR from CSF in high risk patients before start of fingolimod?

- one unusual PML case during fingolimod treatment
Recommendations regarding lymphocyte counts and infections

- contraindications: active/chronic active hepatitis B or C infection, HIV, latent tuberculosis
- test patients at risk before start of fingolimod
- do not stop treatment during normal infections (recovery of lymphocytes would take longer than infection normally lasts, no clear association between lymphocyte counts and infection)
- contact infectiologist when unusual relapse or infection symptoms occur
- no concomitant other immunosuppressive medication, limit steroid treatment to pulse
- lymphocyte limit of 200 is arbitrary, lower numbers can be tolerated, when patient is not showing increased infections
Effect of fingolimod on antibody response in healthy volunteers

Study design:

- This was an exploratory, randomized, double-blind, placebo-controlled, parallel group study comparing the effect of once-daily fingolimod (0.5 mg and 1.25 mg doses) versus placebo on antibody response in healthy subjects.
- 72 healthy subjects as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening underwent randomization.
- 66 of the 72 enrolled completed the study. 6 subjects discontinued the study.
  - The reasons for discontinuation included adverse events (fingolimod 0.5 mg: 2 subjects; fingolimod 1.25 mg: 1 subject), consent withdrawal (fingolimod 1.25 mg and placebo: both 1 subject each) and protocol deviations (1 subject in the placebo group).

Ability to mount increases in T cell-dependent and T cell-independent antibody levels in response to novel antigens is retained in healthy volunteers under fingolimod treatment.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fingolimod 0.5 mg</th>
<th>Fingolimod 1.25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increase in anti-KLH IgG levels from pre-immunisation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2-fold</td>
<td>95.5</td>
<td>100.0</td>
<td>90.5</td>
</tr>
<tr>
<td>&gt;4-fold</td>
<td>90.9</td>
<td>90.9</td>
<td>57.1</td>
</tr>
<tr>
<td><strong>Increase in anti-PPV-23 IgG levels from pre-immunisation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2-fold</td>
<td>86.4</td>
<td>77.3</td>
<td>54.5</td>
</tr>
<tr>
<td>&gt;4-fold</td>
<td>57.1</td>
<td>57.1</td>
<td>40.9</td>
</tr>
</tbody>
</table>

IgG; immunoglobulin G; KLH, keyhole limpet haemocyanin; PPV, pneumococcal polysaccharides vaccine

Schmouder R et al. Mult Scler 2010: P412
Study design:


**Immune response to novel and recall antigen in fingolimod-treated multiple sclerosis patients (VERIFY Study)**

- **Aim of VERIFY study:** To evaluate the immune response in MS patients treated with fingolimod (compared to placebo) against both novel antigen (seasonal influenza vaccine) and recall antigen (tetanus toxoid [TT] booster dose)

- **A 3-month, blinded, randomized, multicenter, placebo-controlled, parallel-group, two arm study that was conducted in 138 patients with relapsing MS**

- **The primary objective was the responder rate to the seasonal influenza vaccine 3 weeks post vaccination**
Responder rate (%) at week 9 (3 weeks after vaccination) and week 12 (6 weeks after vaccination), by treatment group (Full Analysis Set)"
Mounting of vaccine-specific immune responses remains functional in fingolimod-treated patients
Recommendations regarding vaccination

- during and up to two months after fingolimod treatment vaccine response can be reduced

- do not use live vaccines

- vaccinate VZV naive patients before fingolimod start

- start fingolimod one month after vaccination to allow for a normal vaccine response