Immune cell profiles and clinical and safety outcomes with fingolimod in the 12 month FLUENT study of patients with relapsing multiple sclerosis

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Background and objective

- Fingolimod (Gilenya®) is an S1P modulator approved for adult and pediatric patients with RMS[1]
- Fingolimod inhibits $S1P_1$-mediated lymphocyte egress from lymph nodes, impairing infiltration of autoreactive lymphocytes into the CNS[2]
  - However, the effects of fingolimod on specific immune cell subsets remain unclear
- FLUENT study (NCT03257358) investigated the relationship between immune cell subset changes in innate and adaptive immune systems in response to fingolimod

Objective	**Characterize immune cell changes in biomarkers and subtypes of monocytes, neutrophils, and NK, T and B cells, in patients with RMS initiating fingolimod or continuing fingolimod treatment**

CNS, central nervous system; NK, natural killer; RMS, relapsing forms of multiple sclerosis; S1P, sphingosine 1-phosphate receptor

1. Novartis Pharmaceuticals Corporation. Prescribing information. Gilenya®. 2019. Available from: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/gilenya.pdf (Accessed January 13, 2020); 2. Song ZY, *et al*. *PloS One*. 2014;10:e0124923

Methods: Study design

- FLUENT: phase 4, 12 month, prospective, multicenter, nonrandomized, open-label study of fingolimod in adults (≥18 years) with RMS
- Patients stratified according to previous treatment:
  - fingolimod-naive (cohort 1)
  - continuous treatment with fingolimod 0.5 mg/day for ≥2 years (cohort 2)

Assessments

- Primary outcome: change in immune cell subsets from baseline to Month 12
- Secondary outcomes:
  - Patient-Determined Disease Steps
  - serum NfL concentration
  - anti-JCV antibody status
  - incidence of AEs

Analyses

- Primary outcome: analyzed by ANCOVA model with sex and cohort as factors, and disease duration and baseline as covariates
- Secondary outcomes: summarized by descriptive statistics
- Analyses were conducted for all patients completing Month 12 follow-up

AE, adverse event; ANCOVA, analysis of covariance; JCV, John Cunningham virus; NfL, neurofilament light chain; RMS, relapsing multiple sclerosis

Results: Demographics and disease characteristics

- FLUENT included 380 patients
  - fingolimod-naive, n=163
  - continuous-fingolimod, n=217
- Fingolimod-naive participants were younger than continuously treated fingolimod patients
- Proportion of patients with relapses in the past year was greater in fingolimod-naive group than in continuous-fingolimod group

	Cohort 1 Fingolimod-naive (N=163)	Cohort 2 Continuous-fingolimod (N=217)
Age, years, median (range)	41.0 (18-68)	50.0 (24-71)
Female, n (%)	127 (77.9)	158 (72.8)
Race, n (%)		
Caucasian	136 (83.4)	186 (85.7)
Black	22 (13.5)	22 (10.1)
Asian	0	3 (1.4)
Native American	1 (0.6)	2 (0.9)
Unknown	3 (1.8)	1 (0.5)
Other	1 (0.6)	3 (1.4)
Time from diagnosis to first treatment, years, median (range)	3.45 (0.0-33.6)	11.69 (2.3-40.6)
≥1 relapse in the past year, n (%)	101 (62.0)[a]	32 (14.7)[b]
≥1 relapse in the past 2 years, n (%)	116 (71.2)[a]	47 (21.7)[b]

[a]n=162; [b]n=215

Results: Immune cell profile

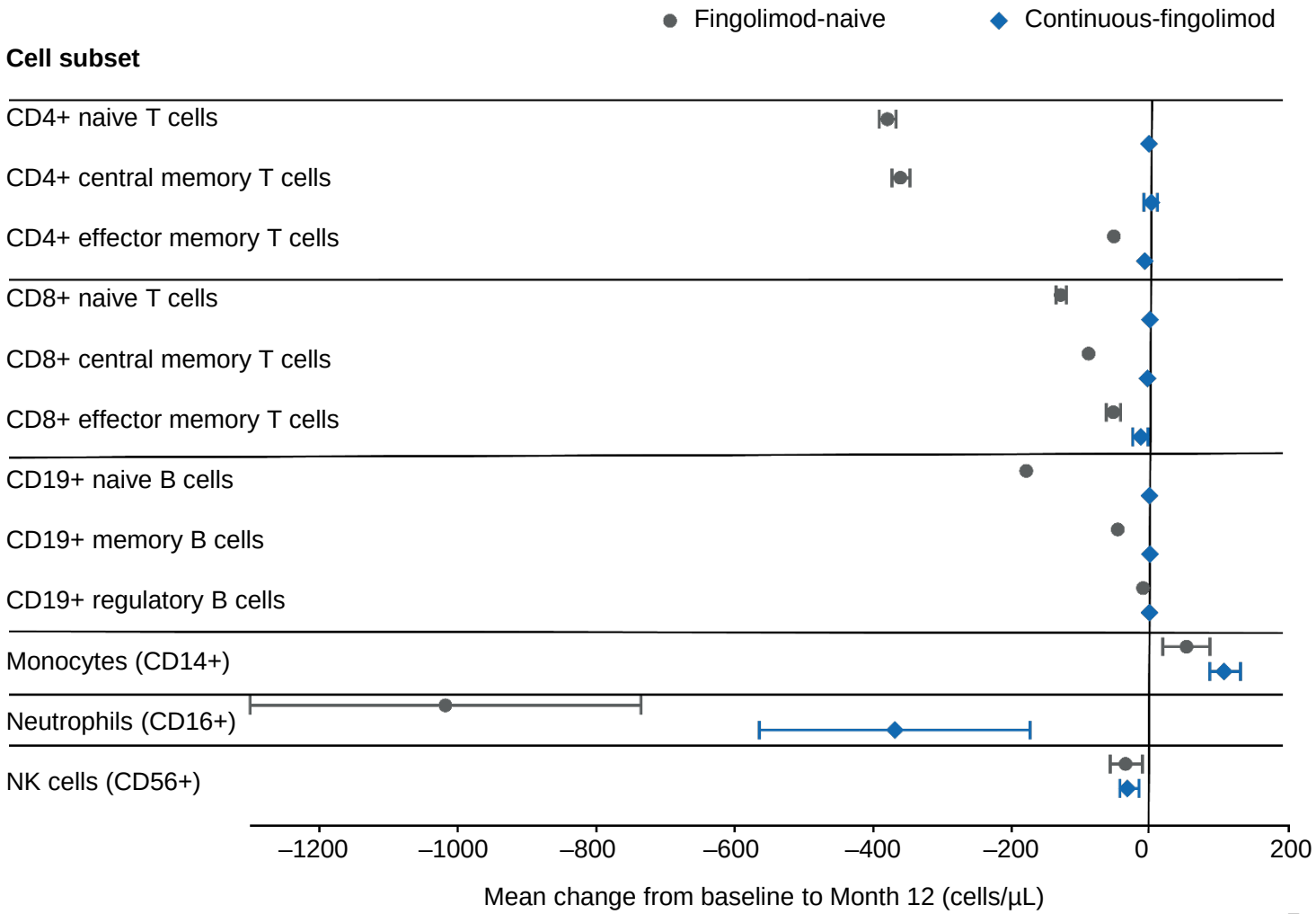
- At baseline, fingolimod-naive patients versus continuous-fingolimod patients have:
  - higher counts of CD4+ T cells, CD8+ T cells and B cells and their respective subsets
  - broadly similar monocyte, neutrophil and NK cell counts

Immune cell subset counts (cells/µl)	Fingolimod-naive (cohort 1)	Fingolimod-treated for ≥2 years (cohort 2)
Adaptive immune cells		
CD4+ naive T cells	404.4 (273.6)	3.4 (20.7)
CD4+ central memory T cells	374.6 (216.4)	16.3 (45.1)
CD4+ effector memory T cells	74.3 (43.6)	22.8 (41.2)
CD8+ naive T cells	150.9 (119.5)	1.8 (8.9)
CD8+ central memory T cells	93.1 (75.2)	5.6 (14.9)
CD8+ effector memory T cells	108.2 (93.3)	63.8 (115.3)
CD19+ naive B cells	201.1 (134.0)	18.1 (33.8)
CD19+ memory B cells	61.8 (74.3)	3.3 (22.6)
CD19+ regulatory B cells	12.3 (12.9)	5.3 (7.7)
Innate immune cells		
Monocytes (CD14+)	329.6 (167.5)	251.7 (118.5)
Neutrophils (CD16+)	4041.4 (1576.7)	3717.9 (1552.9)
NK cells (CD56+)	166.4 (98.2)	181.0 (114.0)

Data are mean (standard deviation)
NK, natural killer

Results: Immune cell profile changes from baseline to Month 12

- From baseline to Month 12, continuous-fingolimod patients had similar numbers of T cell and B cell subtypes
- By contrast, fingolimod-naive patients had reductions from baseline in B cell and T cell subtypes
- Decreases in neutrophil and NK cell counts from baseline to Month 12 were observed for both continuous-fingolimod and fingolimod-naive groups
  - Reductions in neutrophil counts were most pronounced for fingolimod-naive patients
- Monocyte counts increased from baseline to Month 12 in both groups



Data are adjusted least square means and 95% confidence intervals
NK, natural killer

Results: Serum NfL and Patient-Determined Disease Steps

Serum NfL

- Baseline serum NfL concentrations (mean±SD), a biomarker of neuroaxonal damage,[1] were higher in fingolimod-naive patients than in those continuing fingolimod treatment
  - Fingolimod-naive patients, 12.16±11.05 pg/mL; continuous fingolimod, 9.59±7.56 pg/mL
- At Month 12, serum NfL concentrations (mean changes [95% CI]):[a]
  - decreased to 8.57±5.32 pg/mL (−3.73 pg/mL [−6.03,−1.43]) in fingolimod-naive patients
  - increased marginally to 9.78±8.88 pg/mL (+0.67 pg/mL [−0.56, 1.90]) in those previously treated with fingolimod

Patient-Determined Disease Steps

- PDDS scores (patient reported outcome measure that correlates with EDSS scores[2]) remained stable at Month 12 in both cohorts, with changes from baseline of (mean±SD) −0.1±0.9 vs 0.0±0.8
  - Baseline PDDS scores: 1.7±1.9 for fingolimod-naive; 1.8±1.9 for patients previously treated with fingolimod

[a]Comparative statistical analyses were not performed for changes in NfL

CI, confidence interval; EDSS, Expanded Disability Status Scale; NfL, neurofilament light chain; PDDS, Patient-Determined Disease Steps; SD, standard deviation

1. Disanto G, *et al*. *Ann Neurol*. 2017;81:857-870; 2. Learmonth YC, *et al*. *BMC Neurol*. 2013;13:37

Safety

- Anti-JCV antibody index did not change from baseline in either cohort
- Proportion of patients with positive JCV status remained stable at Month 12:
  - Fingolimod-naive, 61%; continuous-fingolimod, 67%
  - Baseline proportions: 57% and 65%, respectively
- Proportions of patients with serious AEs were low in both cohorts
  - Most AEs were more frequently reported in fingolimod-naive patients than in those continuing treatment, except for fall and UTI
- TEAEs and AEs leading to discontinuation occurred in a greater proportion of fingolimod-naive patients than continuous-fingolimod patients

Event, n (%)	Fingolimod-naive (cohort 1; n=163)	Fingolimod-treated for ≥2 years (cohort 2; n=163)
Treatment-emergent AE	89 (54.6)	96 (44.2)
Serious AE	9 (5.5)	12 (5.5)
Treatment-emergent AE leading to treatment discontinuation	20 (12.3)	12 (5.5)
AEs occurring in ≥3% of patients in at least 1 cohort		
Headache	13 (8.0)	4 (1.8)
Lymphopenia	9 (5.5)	1 (0.5)
Pain in extremity	9 (5.5)	3 (1.4)
URTI	8 (4.9)	6 (2.8)
Fatigue	8 (4.9)	3 (1.4)
Anxiety	6 (3.7)	3 (1.4)
Dizziness	6 (3.7)	1 (0.5)
Fall	5 (3.1)	13 (6.0)[a]
Depression	5 (3.1)	2 (0.9)
Hypoesthesia	5 (3.1)	1 (0.5)
Migraine	5 (3.1)	1 (0.5)
Arthralgia	5 (3.1)	6 (2.8)
UTI	1 (0.6)	7 (3.2)

[a]Patients in cohort 2 may have been at a greater risk of falling than those in cohort 1 owing to older age and longer MS duration. Mean baseline age (years): 41 (cohort 1) and 50 (cohort 2); mean baseline MS duration (years): 3.5 (cohort 1) and 11.7 (cohort 2). AE, adverse event; JCV, John Cunningham Virus; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection, UTI, urinary tract infection.

Conclusions

- As expected, given fingolimod's MoA, fingolimod-naive patients initiating treatment experienced marked reductions in CD4+ and CD8+ T cells at 12 months
- Patients who had received fingolimod treatment for at least 2 years showed minor changes in immune cell subsets at 12 months
  - Immune cell subsets were not further reduced with longer term fingolimod treatment
- NfL levels decreased from baseline in the fingolimod-naive cohort
- Anti-JCV antibody index remained unchanged during the study
- Fingolimod was generally well tolerated in both naive and previously treated patients

JCV; John Cunningham virus, MoA, mechanism of action; NfL, neurofilament light chain