

Short term relapse risk after switching from Fingolimod to Ocrelizumab or Cladribine – a retrospective international cohort study

Introduction

Background:

- Information on disease activity when switching MS medication from fingolimod (FTY) to ocrelizumab (OCR)/cladribine (CLAD) is scarce
- Severe return of disease activity has been reported in smaller heterogeneous case series in around 10% of patients (irrespective of following treatment) ^{1,2}
- With increasing number of available MS treatments, MS patients might switch disease modifying treatments for various reasons (pregnancy, side effects, lacking efficacy)

Objective:

- to assess the short-term relapse and disability risk after switching from FTY to OCR or CLAD in patients with relapsing-remitting multiple sclerosis (RRMS)

Design and Methods:

- Patients were recruited from several academic centers (AC) throughout Europe (Germany/Norway) and two national registries:
 - Danish MS Register (DMSR)
 - German MS Register (GMSR)

We included 283 adults with RRMS who stopped FTY and switched to OCR/CLAD

- AC: N_{OCR}=74; N_{CLAD}=31
- DMSR: N_{OCR}=75; N_{CLAD}=15
- GMSR: N_{OCR}=72; N_{CLAD}=16

Exposure was defined as:

- Treatment free switching interval ≤6 months
- Follow up on OCR/CLAD ≥6 months

Outcomes included:

- number of relapses
- annualized relapse rate (ARR)
- new disease activity on MRI scans
- clinical markers of severe disability increase (≥1 EDSS point within 2 years from FTY cessation)

Statistics:

- Descriptive key figures include means and percentages along with 95% (Clopper-Pearson) confidence intervals.
- ARR are compared by using generalized linear models for overdispersed count data including random effects and different observation times as an offset.
- Estimates by data source are combined in a random effects (RE) meta-analysis (REML, assessment of heterogeneity, Forrest plots)

*data were only available for academic centers.

Reference:

¹ Frau et al., 2018, Eur J Neurol., 25(10):1270-1275

² Hatcher et al., 2016, JAMA Neurol., 73(7):790-794

Results

	Baseline characteristics		
	Academic centers (AC)	Danish MS Register (DMSR)	German MS Register(GMSR)
No. of patients N %	105 37.1%	90 31.8%	88 31.1%
Females % [95% CI]	73.3% [63.8-81.5]	68.9% [58.3-78.2]	76.1% [65.9-84.6]
Age at disease onset in years, mean [95% CI]	27.4 [25.3-29.5]	29.6 [27.8-31.4]	26.4 [24.6-28.1]
Symptoms at disease onset N/a % [95% CI]			
motor	16/105 15.2% [9.0-23.6]	29/80 36.3% [25.8-47.8]	18/58 31.0% [19.5-44.5]
visual	29/105 27.6% [19.3-37.2]	18/79 22.8% [14.1-33.6]	31/57 54.4% [40.7-67.6]
sensory	45/105 42.9% [33.2-52.9]	38/55 69.1% [55.2-80.9]	34/65 52.3% [39.5-64.9]
No. of DMTs prior to FTY N %			
Treatment naive	8 7.6%	12 13.3%	21 23.9%
1 DMT	41 39.0%	35 38.9%	28 31.8%
2-3 DMT	45 42.9%	35 38.9%	29 33.0%
4+ DMT	11 10.5%	8 8.9%	10 11.4%
Time on FTY in years, median [range]	1.8 [0.1-7.7]	2.9 [0.1-7.6]	2.7 [0.1-7.9]
Last EDSS under FTY treatment, median [range]	2.0 [0.0-6.5]	2.5 [0.0-7.0]	3.0 [0.0-7.0]
Discontinuation reasons for FTY (multiple choice) N %			
Clinical relapse: 44 41.9%	Contra indication: 1 1.1%	Disease activity: 22 81.5%	
Only MRI activity: 24 22.9%	Disease activity: 51 56.7%	Adverse events: 5 18.5%	
Adverse events: 35 33.3%	Adverse events: 31 34.4%	Missings: 61 69.3 %	
Planning pregnancy: 12 11.4%	Planning pregnancy: 2 2.2%		
Other: 3 2.9%	Other: 5 5.6%		
Age at FTY cessation in years, mean [95% CI]	37.87 [35.57-40.18]	41.31 [39.32-43.30]	40.91 [38.94-42.88]

Table 1: Baseline demographics and disease status at time of FTY cessation stratified by data source. Means and % along with 95% confidence intervals are reported. No. = numbers, 95% CI = 95% confidence interval, DMT = disease modifying therapy, EDSS = Expanded Disability Status Scale, FTY = Fingolimod, N = number of patients, a = available datasets

	Follow-up after FTY discontinuation					
	CLAD N=62			OCR N=221		
	AC	DMSR	GMSR	AC	DMSR	GMSR
No. of patients N %	31 50%	15 24%	16 26%	74 33%	75 34%	72 33%
Length of switching interval in years, mean [95% CI]	0.12 [0.09-0.15]	0.23 [0.17-0.28]	0.17 [0.14-0.20]	0.19 [0.16-0.21]	0.15 [0.13-0.17]	0.18 [0.15-0.20]
Patients with at least one relapse during switching interval N % [95% CI]	4 12.9% [3.6-29.8]	2 13.3% [1.7-40.5]	1 6.3% [0.2-30.2]	17 23.0% [14.0-34.2]	4 5.3% [1.5-13.1]	2 2.8% [0.3-9.7]
Patients with disease activity on brain MRI scan during switching interval N/a % [95% CI]	3/4 75.00% [19.41-99.37]	4/8 50.00% [15.70-84.30]	-	12/32 37.50% [21.10-56.31]	11/32 34.38% [18.57-53.19]	3/7 42.86% [9.90-81.59]
Patients with relapses within 3 months of Switch treatment N % [95% CI]	10 32.26% [16.68-51.37]	1 6.67% [0.17-31.95]	1 6.25% [0.16-30.23]	7 9.46% [3.89-18.52]	3 4.00% [0.83-11.25]	9 12.50% [5.88-22.41]
Patients with relapses within 6 months of switch treatment N % [95% CI]	11 35.48% [19.23-54.63]	1 6.67% [0.17-31.95]	2 12.50% [1.55-38.35]	8 10.81% [4.78-20.20]	4 5.33% [1.47-13.10]	10 13.89% [6.87-24.06]
Total no. of relapses within 6 months of switch treatment	14	1	2	8	5	11
Patients with disease activity on brain MRI scan under switch treatment N/a % [95% CI]	19/29 65.52% [45.67-82.06]	5/11 45.45% [16.75-76.62]	2/11 18.18% [2.28-51.78]	13/55 23.64% [13.23-37.02]	23/62 37.10% [25.16-50.31]	11/43 25.58% [13.52-41.17]
Patients with ΔEDSS ≥1 from end of FTY to last follow-up (max. 2 years;) N/a % [95% CI]	2/24 8.33% [1.03-27.00]	1/8 12.50% [0.32-52.65]	0/12 0.00% [0.0-26.5]	12/63 19.05% [10.25-30.91]	12/58 20.69% [11.17-33.35]	9/43 20.45% [9.80-35.30]
Last EDSS in follow-up (max. 2 years), median [range]	2.0 [1.0-5.0]	2.5 [0.0-4.0]	3.0 [0.0-6.0]	2.5 [0.0-8.0]	3.0 [0.0-7.5]	3.5 [0.0-7.5]

Table 2: Total numbers and measures of disease activity and disease progression stratified by switchers to CLAD and OCR. Percentages and means along with 95% confidence intervals are reported. FTY = Fingolimod, CLAD = Cladribine, OCR = Ocrelizumab, AC = Academic Centers, DMSR = Danish MS Register, GMSR = German MS Register, No. = numbers, 95% CI = 95% confidence interval, EDSS = Expanded Disability Status Scale, switch treatment = CLAD/OCR N = number of patients, a = available datasets

Results:

- Nine (3.18%) patients discontinued switch treatment, four (6.45%) CLAD patients due to disease activity, three (1.36%) OCR patients due to side effects and one (0.45%) OCR patient each due to contra indication and pregnancy planning.

Disclosures:

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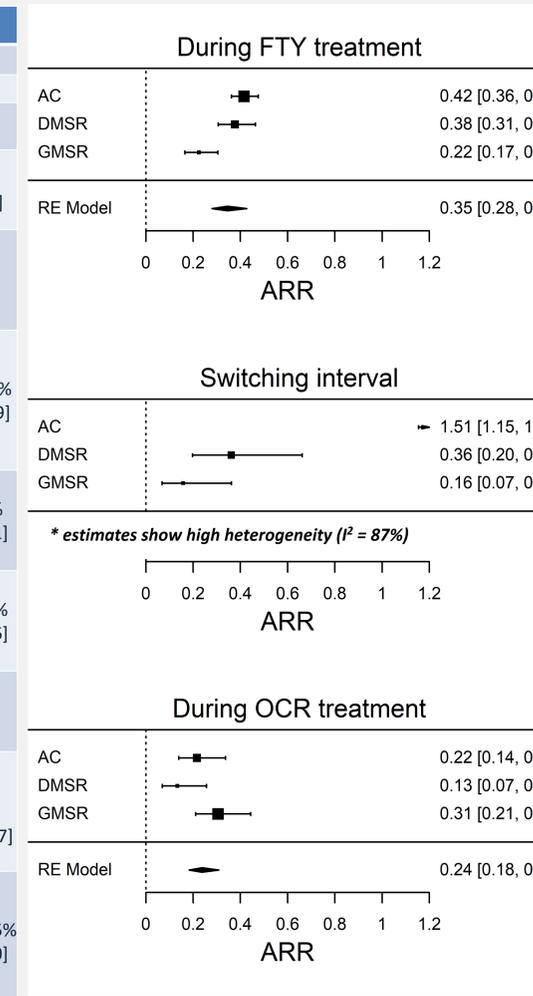


Figure 1: ARR during FTY treatment (top), switching interval (middle), and OCR (bottom) for OCR cohort (N=221). Generalized linear model estimates along with 95% confidence intervals are given per data source as well as RE-meta analysis. FTY = Fingolimod, OCR = Ocrelizumab, AC = academic centers, DMSR = Danish MS register, GMSR = German MS register, ARR = annualized relapse rate

Conclusions

- Around 20% of FTY switchers to OCR or CLAD experienced a relapse
- Most relapses occurred during the treatment free switching interval or the first 3 months on switch treatment
- The relapse risk varied according to the data source and was highest in AC, reflecting potential referral center bias with more severely diseased patients
- Relapse rates were lower after switch to OCR compared to relapse rates under FTY, especially in academic centers, were a large number switched due to lacking efficacy
- Again this reflects a cohort with very active MS
- disease activity on MRI scan was higher in treatment free switching interval than under switch treatment
- disease activity on MRI scan was higher under CLAD than under OCR
- Our data is limited by a relatively small sample size in the CLAD cohort and the retrospective study design.

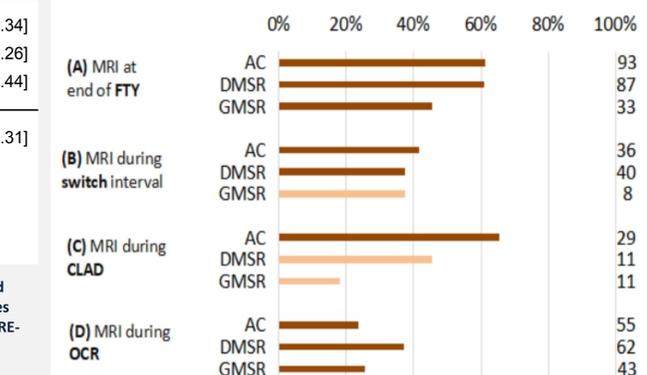


Figure 2: Patients with MRI activity (measured by new GD+ lesions or T2 lesions) in the considered interval (FTY treatment (top), switching interval (second), CLAD treatment (third) and OCR treatment (bottom)) given as percent. Cohort sizes for non-missing values are given to the right. FTY = Fingolimod, CLAD = Cladribine, OCR = Ocrelizumab, AC = academic centers, DMSR = Danish MS register, GMSR = German MS register, MRI = magnetic resonance imaging

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