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Short term relapse risk after switching from natalizumab to ocrelizumab or cladribine – an international cohort study

Introduction

Background:

- The relapse risk after stopping Natalizumab (NTZ) varies between 9 and 80% and seems to be lower after switching to second line drugs as Fingolimod.[1]
- Information on disease activity after switching to newer drugs as Ocrelizumab (OCR)/Cladribine (CLAD) is scarce.
- With increasing number of available multiple sclerosis (MS) treatments, MS patients might switch disease modifying treatments for various reasons (pregnancy/side effects/lacking efficacy).

Objective:

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

Design and Methods:

- Patients were recruited from several academic centers (AC) throughout Germany and two national registries:
  - Danish MS Register (DMSR)
  - German MS Register (GMSR)
- We included 260 adults with RRMS who stopped NTZ and switched to OCR/CLAD
  - AC: N_{OCR}= 66; N_{CLAD}= 4
  - DMSR: N_{OCR}= 61; N_{CLAD}=17
  - GMSR: N_{OCR}=100; N_{CLAD}=12
- 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)
  - clinical markers of severe disability increase (≥1 EDSS points)
  - disease activity on brain MRI scans
    i) during relapse and
    ii) at last follow up visit

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).

Reference:
[1]Prosperini et al. (2019)

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Results

Baseline characteristics

	Academic centers (AC)	Danish MS Register (DMSR)	German MS Register (GMSR)
No. of patients N | %	70 | 27%	78 | 30%	112 | 43%
Females % [95% CI]	77.1% [65.6-86.3]	60.3% [48.5-71.2]	67.9% [58.4-76.4]
Age at disease onset in years, mean [95% CI]	28.8 [26.3-31.3]	31.2 [29.2-33.1]	27.6 [25.8-29.4]
Symptoms at disease onset N/a | % [95% CI]			
motoric	14/70 | 20.0% [11.4-31.3]	16/73 | 21.9% [13.1-33.1]	37/68 | 54.4% [41.9-66.6]
visus	18/70 | 25.7% [16.0-37.6]	20/72 | 27.8% [17.9-39.6]	44/79 | 55.7% [44.1-66.9]
sensory	25/70 | 35.7% [24.6-48.1]	23/36 | 63.9% [46.2-79.9]	54/81 | 66.7% [55.3-76.8]
polysymptomatic	14/70 | 20.0% [11.4-31.3]	-	-
No. of DMTs prior to NTZ N | %			
Treatment naïve	16 | 22,9%	7 | 9.0%	42 | 37.5%
1 DMT	19 | 27,1%	29 | 37.2%	35 | 31.2%
2-3 DMT	26 | 37,1%	34 | 43.6%	30 | 26.8%
4+ DMT	8 | 11,4%	8 | 10.2%	5 | 4.5%
missing	1 | 1,4%	-	-
Time on NTZ in years, median [range]	2.9 [0.2-15.0]	3.6 [0.1-10.7]	3.0 [0.1-12.4]
Last EDSS under NTZ treatment median [range]	2.5 [0.0-6.5]	3.0 [0.0-7.5]	2.0 [0.0-7.5]
Discontinuation reasons for NTZ (multiple choice) N | % or N/a | %	Clinical relapse: 16 | 22.9% Only MRI activity: 2 | 2.9% Adverse events: 1 | 1.4% Planning pregnancy: 1 | 1.4% Other (liver, jcv, etc.): 52 | 74.3%	Disease activity: 4 | 5.1% Practical issues: 4 | 5.1% Antibodies: 12 | 15.4% Adverse events: 3 | 3.8% JC Virus: 26 | 33.3% Other reason: 29 | 37.2%	Other reason (jcv): 12/29 | 41.4% Disease activity: 9/29 | 31.0% Adverse events: 2/29 | 6.9% Patient's wish: 6/29 | 20.7%
Age at NTZ cessation in years, mean [95% CI]	37.92 [35.06-40.78]	44.32 [42.03-46.61]	39.57 [37.56-41.59]

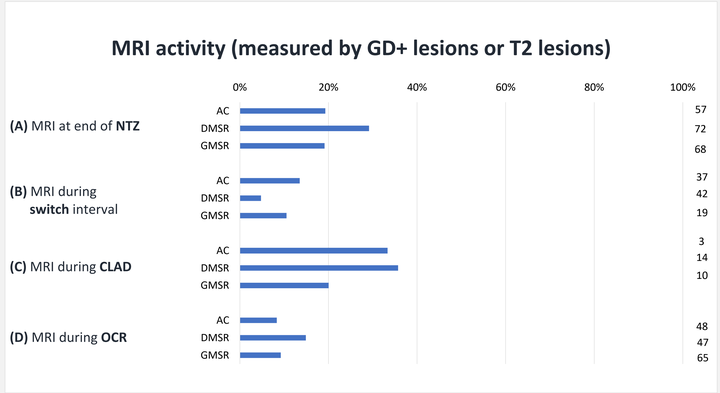
Table 1: Baseline demographics and disease status at the end of NTZ stratified by data source. Means and percentages (%) along with 95% confidence intervals as well as medians along with ranges are reported.
No. = numbers, 95% CI = 95% confidence interval, N = number of patients, a = available data sets, DMT = disease modifying therapy, EDSS = Expanded Disability Status Scale, NTZ = Natalizumab, jcv = John Cunningham (JC) Virus, liver = elevated liver enzymes

- For one patient on OCR as well as one patient on CLAD disease activity was reported.
- For two patients on OCR side effects were reported as discontinuation reason.

Follow-up after NTZ discontinuation

	CLAD N=33			OCR N=227		
	AC	**DMSR**	**GMSR**	**AC**	**DMSR**	**GMSR**
No. of patients N | %	4 | 12%	17 | 52%	12 | 36%	66 | 29%	61 | 27%	100 | 44%
Length of switching interval in years, mean [95% CI]	0.20 [0.06-0.35]	0.16 [0.12-0.21]	0.22 [0.15-0.29]	0.17 [0.15-0.19]	0.17 [0.15-0.19]	0.20 [0.18-0.23]
Patients with at least one relapse during switching interval N | % [95% CI]	0 | 0%	0 | 0% [0.0-19.5]	1 | 8.3% [0.2-38.5]	3 | 4.5% [0.9-12.7]	1 | 1.6% [0.0-8.8]	7 | 7.0% [2.9-13.9]
Patients with disease activity on brain MRI scan during switching interval N/a | % [95% CI]	-	1/9 | 11.11% [0.28-48.25]	-	5/36 | 13.89% [4.67-29.50]	1/33 | 3.03% [0.08-15.76]	2/16 | 12.50% [1.55-38.35]
Patients with relapses within 3 months of Switch treatment N | % [95% CI]	1 | 25.00%	1 | 5.88% [0.15-28.69]	3 | 25.00% [5.49-57.19]	3 | 4.55% [0.95-12.71]	0 | 0%	5 | 5.00% [1.64-11.28]
Patients with relapses within 6 months of switch treatment N | % [95% CI]	1 | 25.00%	1 | 5.88% [0.15-28.69]	3 | 25.00% [5.49-57.19]	7 | 10.61% [4.37-20.64]	2 | 3.28% [0.40-11.35]	7 | 7.00% [2.86-13.89]
Total no. of relapses within 6 months of switch treatment	1	1	3	7	2	9
Patients with disease activity on brain MRI scan under switch treatment N/a | % [95% CI]	1/3 | 33.33% [0.84-90.57]	5/14 | 35.71% [12.76-64.86]	2/10 | 20.00% [2.52-55.61]	4/48 | 8.33% [2.32-19.98]	7/47 | 14.89% [6.20-28.31]	6/65 | 9.23% [3.46-19.02]
Patients with Δ EDSS from end of NTZ to last follow-up (max. 2 years; ΔEDSS ≥1) N/a | % [95% CI]	-	1/12 | 8.33% [0.21-38.48]	1/10 | 10.00% [0.25-44.50]	7/62 | 11.29% [4.66-21.89]	4/45 | 8.89% [2.48-21.22]	14/71 | 19.72% [11.22-30.86]
Last EDSS in follow-up (max. 2 years) median [range]	-	2.0 [0.0-6.0]	1.5 [0.0-6.5]	2.5 [0.0-6.5]	3.0 [0.0-6.5]	3.0 [0.0-8.0]

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 as well as medians along with ranges are reported.
NTZ = Natalizumab, CLAD = Cladribine, OCR = Ocrelizumab, AC = Academic Centers, DMSR = Danish MS Register, GMSR = German MS Register, EDSS = Expanded Disability Status Scale, switch treatment = CLAD/OCR, MRI = magnetic resonance imaging, No. = numbers, 95% CI = 95% confidence interval, N = number of patients, a = available data sets



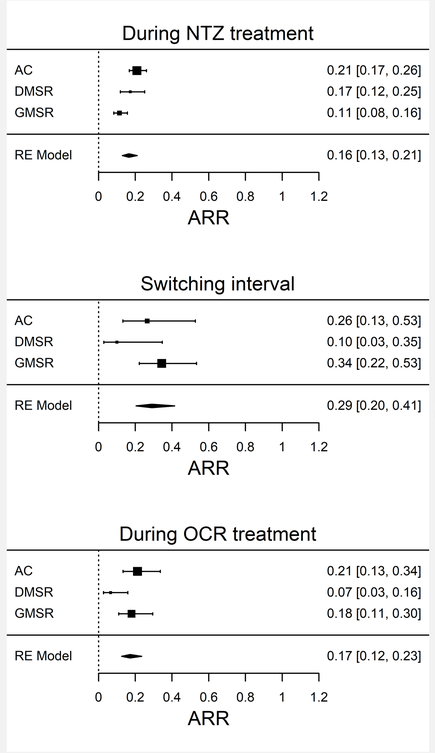


Figure 1: ARR during NTZ treatment (top), switching interval (middle), and OCR (bottom) for OCR cohort (N=227). Generalized linear model estimates along with 95% confidence intervals are given per data source as well as RE-meta analysis.
NTZ = Natalizumab, OCR = Ocrelizumab, ARR = annulized relapse rate, AC = Academic Centers, DMSR = Danish MS Register, GMSR = German MS Register, RE = random effects, ARR = annulized relapse rate

Figure 2: Patients with MRI activity (measured by GD+ lesions or T2 lesions) in considered interval (under NTZ treatment, medication free switching interval, under CLAD treatment, under OCR treatment). Cohort sizes for non-missing values are given to the right.
NTZ = Natalizumab, CLAD = Cladribine, OCR = Ocrelizumab, AC = academic centers, DMSR = Danish MS register, GMSR = German MS register, ARR = annualized relapse rate, MRI = magnetic resonance imaging, GD+ = gadolinium enhancing

Conclusions

- The overall ARR during the treatment free switching interval was low in our cohort but varied by data source (lowest in the DMSR).
- ARRs under NTZ treatment, treatment free switching interval and on OCR treatment were not statistical significantly different.
- We observed few relapses most of them occurred in the first 3 months after switch to CLAD, whereas in the OCR switch group most relapses occurred between 3-6 months after treatment.
- EDSS worsening ≥ 1 was rare therefore the effect estimates lack precision.
- Disease activity measured by MRI was low for OCR, while for CLAD cohort sizes were small.
- Our data is limited by small sample sizes in the CLAD cohort and the retrospective study design.

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