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Disability progression after switching from natalizumab to fingolimod or injectable therapies: a NARCOMS analysis

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Background

- Natalizumab is an effective treatment against disability progression in RRMS:
  - In AFFIRM, natalizumab decreased the risk of 6-month confirmed disability progression by 54% compared to placebo.[1]
  - In the 5-year interim analysis of TOP, 84% of natalizumab patients were free of 6-month confirmed disability progression.[2]
- After 2 years of natalizumab, the risk of PML increases in anti-JCV antibody positive patients, which may prompt evaluation of treatment options at that time.[3]
- Disability progression risks associated with transitioning treatment after 2 years of natalizumab have not been fully determined.

RRMS=relapsing remitting multiple sclerosis; TOP=TYSABRI Observational Program; PML=progressive multifocal leukoencephalopathy; [1]Polman CH, et al. *N Engl J Med* 2006;354:899-910; [2]Butzkueven H, et al. JNNP 2014;doi: 10.1136/jnnp-2013-306936.[3]Bloomgren, et al. *N Engl J Med* 2012;366:1870-80

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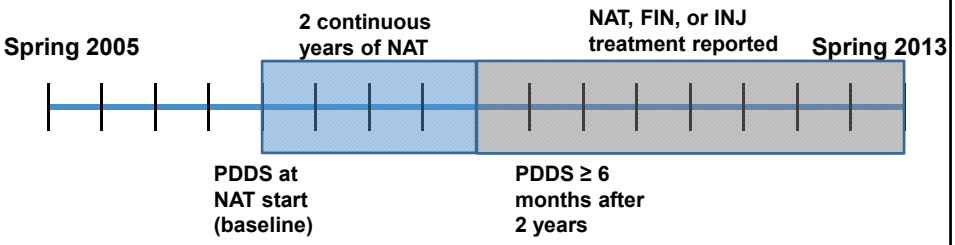
Objective and study design

- Retrospectively compare disability progression, measured by increase in Patient Determined Disease Steps (PDDS)
- NARCOMS participants, after 2 years on natalizumab:
  - remained on natalizumab (NAT) or
  - transitioned to fingolimod (FIN) or
  - transitioned to injectable therapies (INJ: GA or IFNβ)



GA=glatiramer acetate; IFNβ=interferon-beta

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PDDS

- The NARCOMS registry participants report disability in Patient-Determined Disease Steps (PDDS):
  - 0 = Normal
  - 1 = Mild disability (little to no effect on lifestyle)
  - 2 = Moderate disability (but no walking limitations)
  - 3 = Gait disability
  - 4 = Early cane (required for 3 blocks)
  - 5 = Late cane (required for 25 feet)
  - 6 = Bilateral support (required for 25 feet)
  - 7 = Wheelchair / scooter
  - 8 = Bedridden

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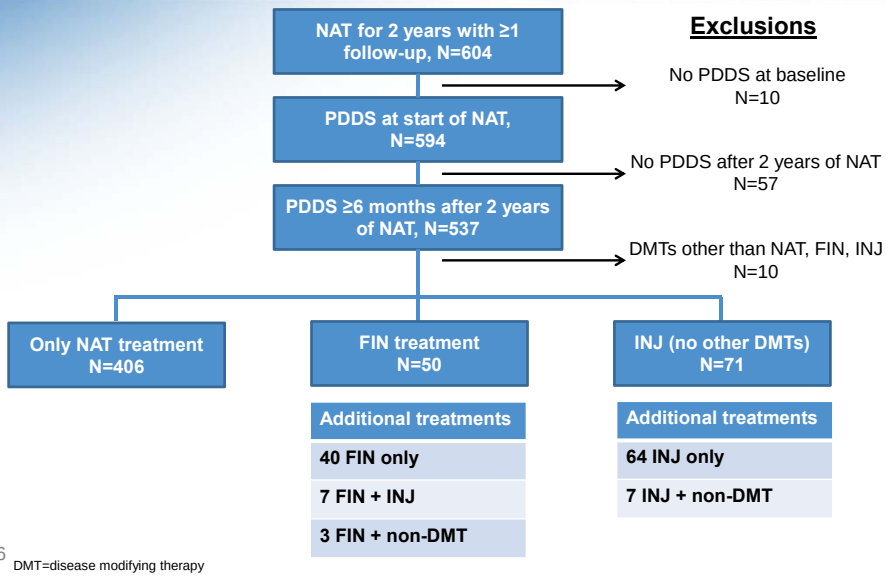
Participant disposition



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DMT=disease modifying therapy

Characteristics at start of natalizumab

	NAT N=406	FIN N=50	INJ N=71	*p*-value
Age, years, mean (SD)	49.4 (9.3)	49.1 (8.4)	50.0 (8.8)	0.8858
Sex, % Female	79.5	70.0	81.7	0.2489
Race, % Caucasian	93.6	88.0	93.0	0.2992
Employment, % with	38.0	44.0	38.0	0.7104
Health insurance, % with	97.8	98.0	98.6	>0.9999
Age at diagnosis, years, mean (SD)	36.4 (9.4)	36.6 (9.0)	36.5 (9.0)	0.9614
Relapse in prior 6 months, % Yes	20.4	16.0	19.7	0.9570
PDDS, mean (SD) median (range)	3.4 (2.1) 3 (0-8)	3.6 (2.0) 4 (0-7)	3.9 (2.3) 4 (0-7)	0.1334

7 SD=standard deviation

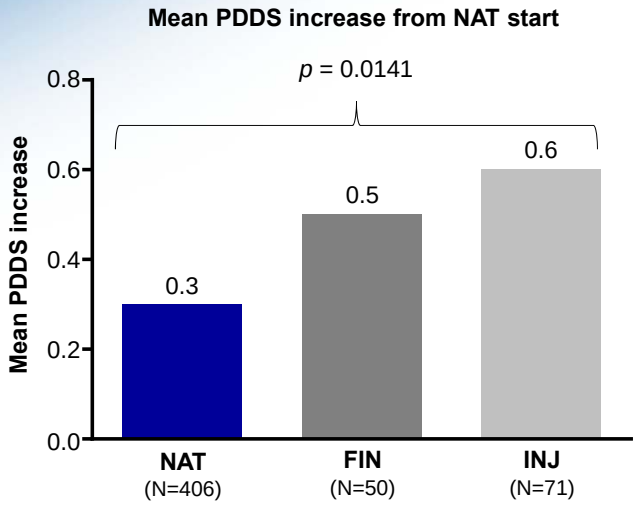
Total follow-up time

	NAT N=406	FIN N=50	INJ N=71	*p*-value
Total follow-up, months, mean (SD) median (range)	 45.6 (16.2) 48 (12-72)	 52.9 (14.4) 54 (18-72)	 57.7 (12.4) 60 (24-72)	 <0.0001
Follow-up after treatment transition, months, mean (SD) median (range)	 NA NA	 13.8 (10.0) 12 (0-42)	 20.4 (13.9) 18 (0-54)	 0.0123

- Those who transitioned to FIN or INJ had longer total follow-up time, including the initial 2 years on NAT.
- Those that transitioned to INJ had longer follow up time after DMT change compared to FIN.

8 NA=not applicable

Mean PDDS increase was lower in the NAT treatment group



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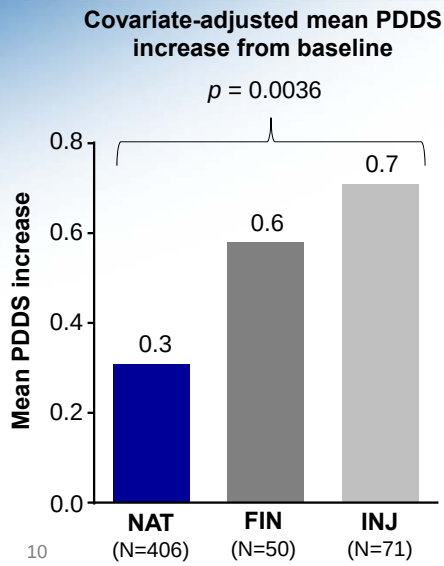
Group differences in PDDS increase remained after covariate adjustment



- Predictors of increased PDDS worsening were:
  - Older age ($p = 0.0014$)
  - Male sex ($p = 0.0235$)
  - Lower baseline PDDS ($p < 0.0001$).
- Follow-up time was not significantly related to PDDS change ($p = 0.6930$).

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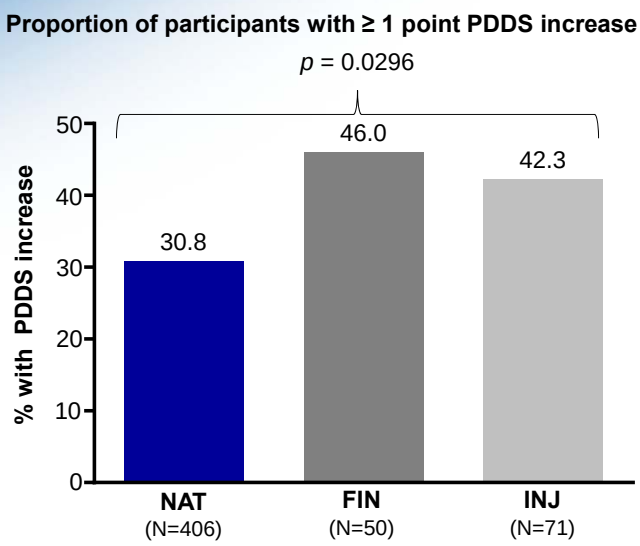
PDDS increase occurred in a smaller proportion of participants in the NAT group



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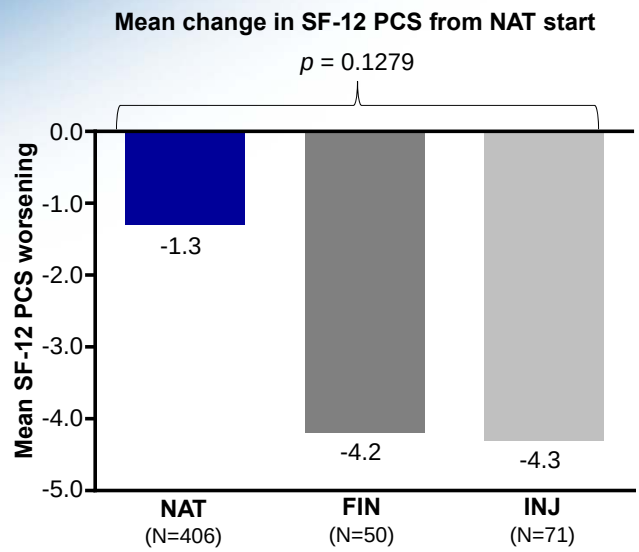
SF-12 PCS worsened significantly in FIN and INJ



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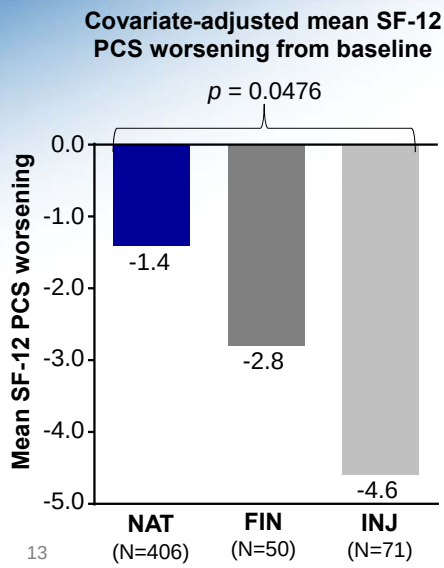
SF= short form; PCS= physical component score

Covariate adjusted group differences in mean SF-12 PCS change



- Predictors of SF-12 PCS worsening were:
  - Older age ($p < 0.0001$)
  - Higher baseline SF-12 PCS ($p < 0.0001$).
- Follow-up time ($p = 0.53$) and sex ($p = 0.44$) were not significantly related to SF-12 PCS change.

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Propensity score paired analysis

- Propensity score pairing reduces potential bias in retrospective studies by selectively comparing participants with balanced baseline characteristics.
  - Propensity scores derived from age, sex, starting PDDS score, and prior relapse activity were used to pair participants.

Characteristic		NAT, N=50	FIN, N=50	NAT, N=45	INJ, N=45
PDDS, n (%):	0-2	15 (30)	15 (30)	11 (24)	11 (24)
	3-5	24 (48)	24 (48)	21 (47)	21 (47)
	6-7	9 (18)	9 (18)	12 (27)	12 (27)
Relapse in prior 6 months, n (%):	No	34 (68)	34 (68)	33 (73)	33 (73)
	Yes	8 (16)	8 (16)	7 (16)	8 (18)
Sex, n (%):	Female	33 (66)	33 (66)	37 (82)	39 (87)
Age:	mean (SD)	49.8 (6.9)	49.1 (8.4)	50.1 (7.9)	49.5 (8.1)

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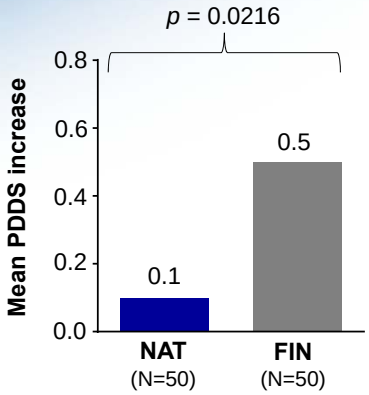
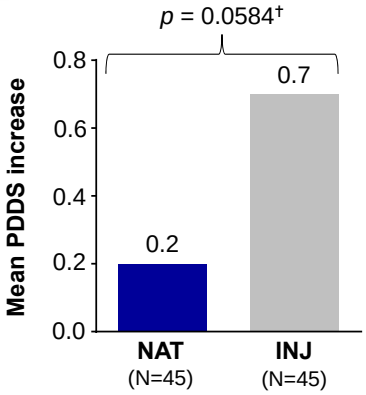
Observed lower mean PDDS increase in the NAT group

Mean PDDS increase for paired NAT-FIN participants



Mean PDDS increase for paired NAT-INJ participants



†*p*-values are not significant after correcting for multiple comparisons

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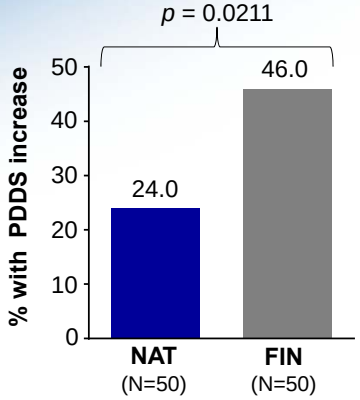
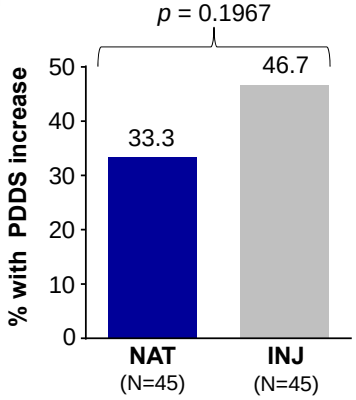
Observed fewer participants with PDDS increase in the NAT group

Proportion of paired NAT-FIN participants with PDDS increase



Proportion of paired NAT-INJ participants with PDDS increase



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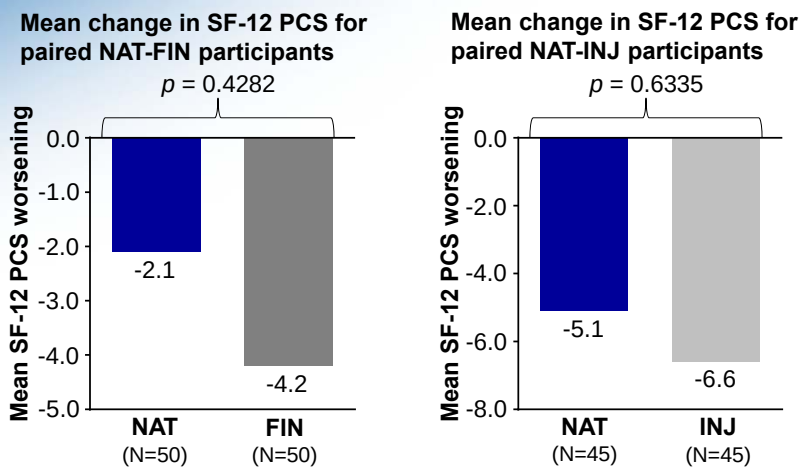
Observed less mean SF-12 PCS worsening in the NAT group



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Conclusions

- Transitioning off natalizumab after 2 years was associated with a significant increase in the likelihood of participant-reported disability progression and increased mean disability.
- Consistent with PDDS observations, transitioning off natalizumab was associated with patient reported SF-12 PCS worsening.
- Similar findings were observed using a propensity score paired analysis, but the differences were not statistically significant.

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