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Combining randomized trials and observational studies data for comparison of treatment effects:

An application to disease modifying therapies for multiple sclerosis

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Disclosures

- This research was funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland
- The following personal or financial relationships relevant to this presentation existed during the prior 12 months and/or during the conduct of the study:
  - E. Muros-Le Rouzic, L. Craveiro – Employee of and shareholder in F. Hoffmann-La Roche Ltd
  - S. Yiu – Employee of Roche Products Ltd.
  - C. Bernasconi - Consultant for F. Hoffmann-La Roche Ltd.
  - F. Model - Employee and shareholder of F. Hoffman-La Roche Ltd at the time of this study; Currently employee of Denali Therapeutics.
  - Y. Heer, V. Tozzi, P. van Hoevell - Employee of PricewaterhouseCoopers; contracted to perform statistical projects for NeuroTransData at the time of this study.
  - S. Braune - Received honoraria from Kassenärztliche Vereinigung Bayerns and health maintenance organisations; from Biogen, Merck, NeuroTransData, Novartis, and Roche; also received honoraria and expense compensation as a board member of NeuroTransData
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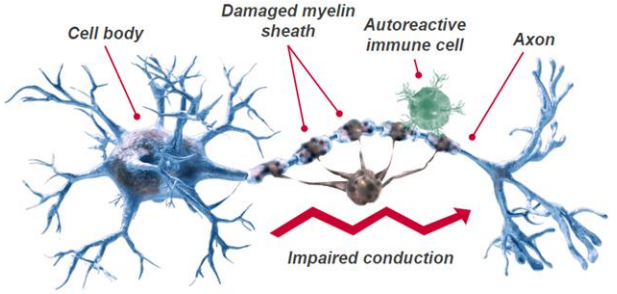
Background

- Multiple Sclerosis (MS)
  - Chronic, immune-mediated disease of the CNS characterised by inflammation, demyelination and degenerative changes
  - Neurological symptoms (relapses) and accumulating permanent disability
- Affects >2 Mio individuals worldwide
- Heterogeneous disease, conventionally defined as either relapsing or progressive phenotypes



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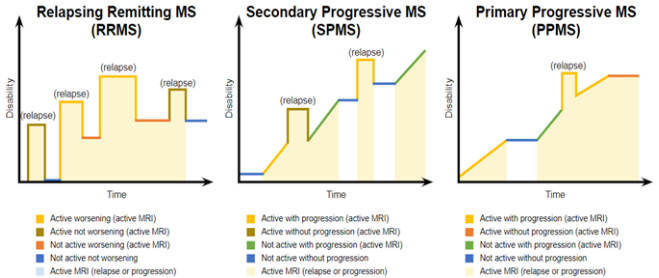


Lublin FD, *et al. Neurology* 2014;83:278–86

Rationale

- Ocrelizumab (OCR)
  - Humanized anti-CD20+ monoclonal antibody
  - In patients with relapsing form of MS (RMS), clinical benefit demonstrated vs. interferon β-1a (IFN β-1a) in phase 3 randomised controlled trials (RCTs) [1]
  - No head-to-head RCTs directly compared OCR vs. other disease-modifying therapies (DMTs)
- High quality real-world observational studies are increasingly used for comparative effectiveness research in MS
- Datasets capturing OCR use in real-world settings remain limited in sample size, treatment exposure and duration of follow-up due to recent approval (USA end-2017, EU early-2018)

[1]Hauser SL, et al. N Engl J Med 2017;376:221–34. ClinicalTrials.gov identifiers: NCT01247324 and NCT01412333

Objectives

To explore the combination of clinical trials and real-world data for comparative effectiveness analysis of the treatment effect of multiple DMTs in patients with RMS.

Data sources

Clinical trial data

- Pooled data from pivotal phase 3 OPERA I & II RCTs[1] and open-label extension (OLE) phase

Real-world data

- NeuroTransData (NTD) registry[3]
  - Germany-wide network of neurologists and psychiatrists specialists
  - Includes ~25,000 patients with MS
  - Captures demographics, clinical history, patient-related outcomes and clinical variables in real-time during clinical visits (average of 3.5 visits per patient each year)

[1]Hauser SL, et al. N Engl J Med 2017;376:221–34; [2]Polman CH, et al. Ann Neurol. 2011;69(2):292-302; [3]Braune S, et al. BMJ open. 2021;11(8):e042480-e042480

Study population

Clinical trial data

- All patients randomised to IFN β-1a or OCR arms excluding US patients
  - Non-US population was 64% European ⇨ more comparable to German NTD population
  - Treatment-by-subgroup interaction observed for body mass index (BMI) on disability outcome between US and ex-US patients ⇨ BMI not systematically collected in NTD Registry to adjust for such interaction

Real-world data

- RMS patients aged ≥18 years, index therapy initiated after 1 Jan 2009, neurological stability at index therapy (no relapse nor ongoing treatment with steroids 8 weeks prior to index therapy)
  - Index therapies: IFN β-1a, natalizumab, glatiramer acetate, fingolimod, dimethyl fumarate, teriflunomide

Methods (1)

Comparative approach	• Use of patient-level data • Propensity score matching with 1:1 pair-matching ratio • 5-to-1 digit greedy nearest neighbor algorithm, no caliper restriction
Covariates balance assessment	• Summary statistics of baseline covariates pre- and post-matching • Standardized mean difference (0.2 threshold) • Density functions of propensity score distribution pre- and post-matching
Outcomes	• Time to first relapse • Time to onset of 24-week confirmed disability progression (24W-CDP)
Follow-up	• Analyses conducted over 288 weeks (5.5 years) of total follow-up from OCR RCTs double-blind period and OLE phase

Methods (2)

Statistical analysis	• Intention-to-treat approach • Cox proportional hazard model • Treatment effects reported as hazard ratios with 95% confidence intervals (2-sided tests) • Kaplan-Meier plots • Analyses were exploratory with no adjustment for multiple comparisons applied

Censoring	• Patient censoring
	  ○ In NTD applied at time of registry discontinuation, when switching to OCR or other anti-CD20 therapy or or at end of follow-up whichever came first
	  ○ For OCR cohorts, data until treatment discontinuation was used

Sensitivity analysis	• Presence/absence of Gd+ lesions not used as a matching factor

Matching factors

Covariates associated with both treatment allocation and outcome were selected to reduce bias of the effect estimation based on empirical clinical knowledge and published evidence[1]

	Age	Biological Sex	Disease duration	EDSS (baseline*)	Relapses in previous year	Previous treatment	Gd+ lesions (baseline*)
	Continuous	Dichotomous	Ordinal	Continuous	Ordinal	Dichotomous	Dichotomous
Time to 1st relapse	X	X	X	X	X	X	X
Time to 24-week CDP	X	X		X	X	X	

Biological sex: Male vs. Female; Time since symptom onset: ≤ 3 years, > 3 to ≤ 5 years, > 5 to ≤ 10 years, >10 years; Previous treatment: Yes vs. No; Gadolinium-enhancing (Gd+) lesions: Present vs. Not present; EDSS, Expanded Disability Status Scale
*EDSS or MRI measurements collected within a window of +/-3 months relative to index-therapy therapy initiation

[1]Laplaud D-A, et al. Comparative effectiveness of teriflunomide vs dimethyl fumarate in multiple sclerosis. Neurology. 2019;93(7):e635

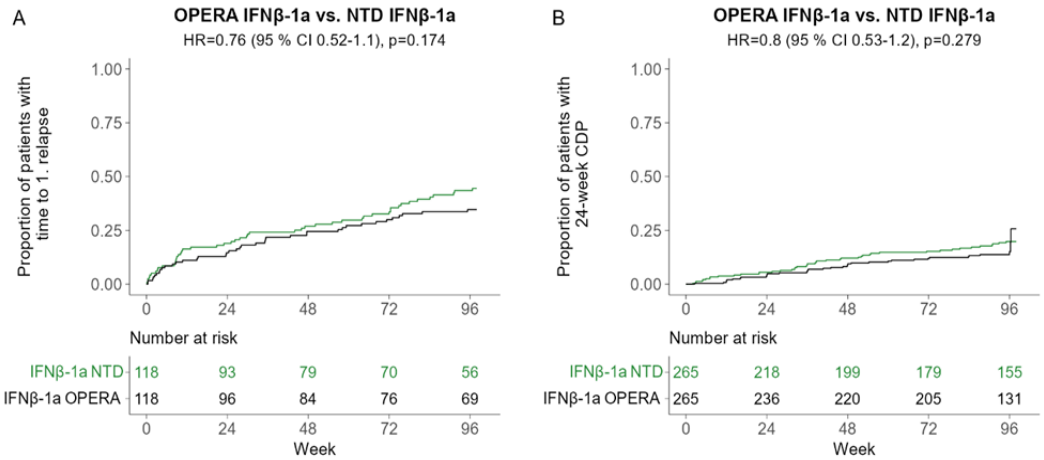
Results

- 6 distinct paired-matched cohorts were built for each outcome
  - Relapse outcome: pair-matched cohorts ranged from 111:111 to 185:185 patients
  - Disability progression: pair-matched cohorts ranged from 200:200 to 331:331 patients
  - Lower sample size in relapse outcome due to use of Gd+ lesions as matching factor
- Matching procedure resulted in cohorts overall well-balanced for baseline covariates and matching factors (all SMDs <0.2)

Results - Feasibility assessment

Exchangeability of clinical trials and real-world datasets assess

- Compare outcomes in OCR RCTs vs. NTD paired-matched IFN β-1a cohorts over 2-years OCR RCTs double-blind period
- No significant difference observed for time to first relapse or time to 24W-CDP
- Numerical trend of fewer relapses and disability events in IFN β-1 treated patients in OCR RCT matched cohort



Results - Comparative analyses

OCR treatment was associated with statistically significant risk reduction in time to first relapse or disability vs. any treatment pathways in NTD, regardless of each index DMT

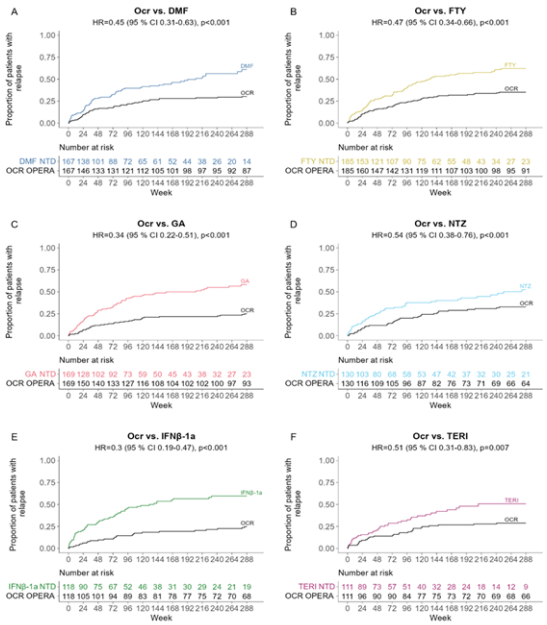
- Similar results for relapse outcome in sensitivity analysis without Gd+ lesions as a matching factor

OCR vs. Index therapy line in NTD registry	Time to first relapse				Time to 24W-CDP			
	N	HR	95% CI	*p-value*	N	HR	95% CI	*p-value*
DMF	167:167	0.45	0.31-0.63	*<0.001*	328:328	0.64	0.44-0.92	*0.015*
FTY	185:185	0.47	0.34-0.66	*<0.001*	252:252	0.66	0.44-0.98	*0.039*
GA	169:169	0.34	0.22-0.51	*<0.001*	331:331	0.67	0.47-0.95	*0.026*
NTZ	130:130	0.54	0.38-0.76	*<0.001*	200:200	0.66	0.43-1.00*	*0.048*
IFN β-1a	118:118	0.30	0.19-0.47	*<0.001*	264:264	0.51	0.35-0.72	*<0.001*
TERI	111:111	0.51	0.31-0.83	*0.007*	222:222	0.61	0.39-0.95	*0.029*

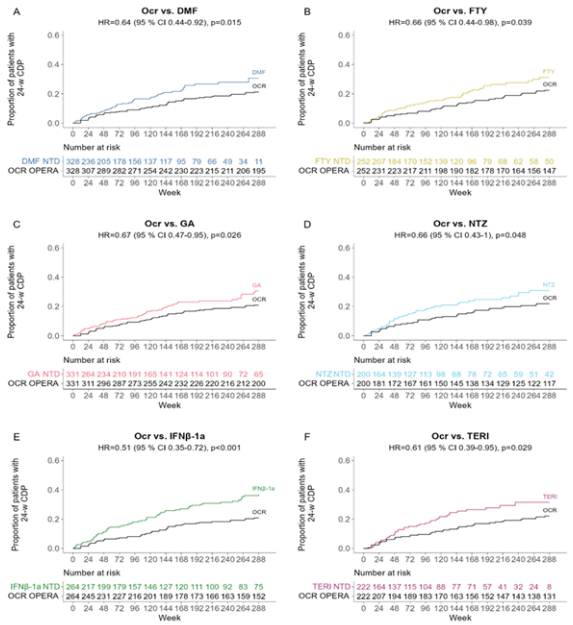
* Note: the 3-digit 95% CI was (0.431-0.996) and the upper limit was rounded to 1.00, however 95% did not include the 1.0 value. 24W-CDP, 24-Week Confirmed Disability Progression; CI, Confidence Interval; DMF, dimethyl fumarate; FTY, fingolimod; GA, glatiramer acetate; HR, Hazard Ratio; IFN β-1a, interferon β-1a; N, number; NTD, NeuroTrans Data Registry; OCR, ocrelizumab; NTZ, natalizumab; TERI, teriflunomide

Results - Comparative analyses

Time to first relapse



Disability outcome

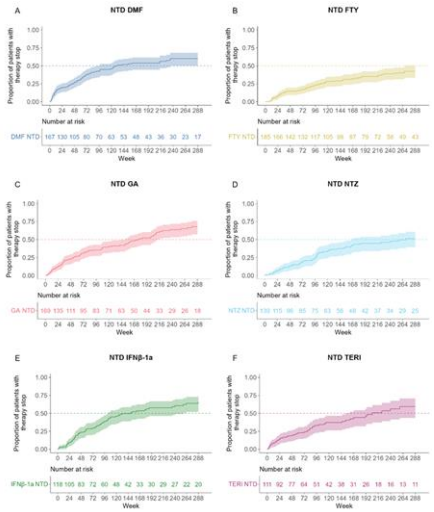


CI, Confidence Interval; DMF, dimethyl fumarate; FTY, fingolimod; GA, glatiramer acetate;HR, Hazard Ratio; IFN β-1a, interferon β-1a NTD, NeuroTrans Data Registry; NTZ, natalizumab; OCR, ocrelizumab; TERI, teriflunomide

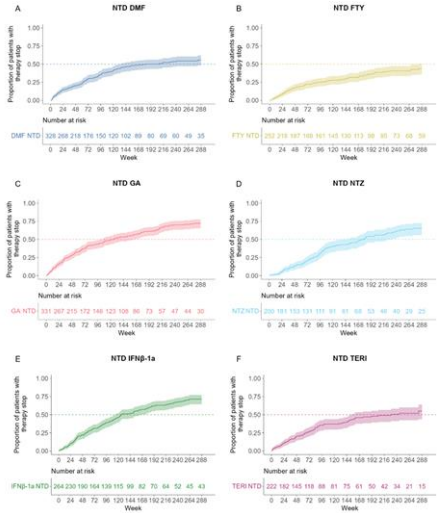
Results - Treatment discontinuations / switches

Over observation period of 5.5 years, ≥50% of patients in nearly all NTD matched cohorts discontinued initial index therapy for each outcome

Relapse outcome



Disability outcome



Discussion

Merging patient-level data from trials and real-world studies remains largely unexplored in MS[1]

Strengths	Limitations

• High data quality of real-world NTD registry
  ○ Matching factors incl. brain imaging lesions data
  ○ Density of clinical visits/assessments
  ○ Clear outcome definitions, certified raters for disability
• Feasibility assessment of comparative approach for baseline covariates and outcomes
• ITT framework
  ○ Account for dynamic/heterogeneous treatment pathways in real-world setting and mitigate informative censoring
	• Require patient-level data sharing with challenges for data privacy and secondary use of data
	• PSM resulted in selection of narrower population, potentially compromising generalizability of results
	• Control only for measured confounders at baseline
	• Use of DMTs followed real-world treatment policy principles, potential for attrition bias
	• Representativeness of NTD registry compared to other MS centers might be limited

[1]Signori A, et al. Cladribine vs other drugs in MS. Neurology - Neuroimmunology Neuroinflammation. 2020;7(6):e878.

Conclusion

- Combining patient level-data from RCTs and real-world datasets represent an option to address knowledge gap arising from the absence of head-to-head clinical trials comparing the clinical efficacy of multiple DMTs for MS
  - Could prove particularly useful at the time of approval of a new DMT, e.g., to inform decision-making for access/reimbursement, treatment guidelines and policies

- Future research
  - Explore other methods accounting for time-dependent confounders (e.g., treatment status and allocation at any time point) to further assess the effect of DMTs conditional on treatment persistence

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