

IMPACT OF NON-RANDOMISED DROPOUT ON TREATMENT SWITCHING ADJUSTMENT IN THE RELAPSING-REMITTING MULTIPLE SCLEROSIS CLARITY TRIAL AND THE CLARITY EXTENSION STUDY

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Objectives Treatment switching adjustment methods are often used to adjust for switching in oncology randomised controlled trials (RCTs). Methods can also be applied to adjust for treatment switching in other settings. We apply statistical methods to adjust for treatment switching in the combined CLARITY and CLARITY Extension studies, to estimate a longer term treatment effect of 3.5 mg (low-dose) cladribine tablets compared with placebo in patients with relapse-remitting multiple sclerosis. We apply the rank preserving structural failure time model (RPSFTM), which relies on a randomisation assumption that may not hold in the context of CLARITY when combined with CLARITY Extension. We test the validity of RPSFTM results using a novel adjustment method that does not rely on randomisation.

CLARITY and Extension trial design

Figure 1 depicts the treatment pathways for patients randomised to receive placebo or 3.5 mg (low-dose) cladribine in CLARITY. See Bell Gorrod, et al (2017) for more details.¹ Table 1 summarises the number of patients which entered into CLARITY and CLARITY extension, by treatment group.

Limitations of the RPSFTM

39% of patients that were randomised to receive 3.5 mg (low-dose) cladribine or placebo in CLARITY did not enrol in the CLARITY extension study. If drop-out is related to prognosis, treatment received or capacity to benefit, the randomisation assumption will not hold.²

Adjusting for bias from switching and drop-out

Data were collected on patient characteristics at baseline and throughout CLARITY and CLARITY extension. This allowed us to apply a propensity score matching (PSM)³ adjustment method combined with inverse probability of censoring weights (IPCW).⁴ These methods do not rely on the randomisation assumption, however PSM relies on common support and conditional independence assumptions, and the IPCW relies on a no unmeasured confounders assumption. Hence, there must be sufficient overlap in the characteristics of the patients, and all relevant prognostic characteristics must be included in the model.

Steps of the PSM + IPCW adjusted analysis:

1. Obtain matched samples of CLARITY LL and CLARITY PP, matched to the extension "PPLL no previous event" group based on patient characteristics
2. Assess how well the matching methods perform
3. Use an accelerated failure time model to estimate the cladribine treatment effect in the form of an acceleration factor (AF) from our matched samples i.e. matched CLARITY LL vs matched CLARITY PP
4. Adjust the PPLL arm of the data by applying the AF to switching patients, to create a counterfactual dataset
5. Calculate inverse probability of censoring weights based on Fewell, et al (2004)⁵
6. Estimate a treatment switching adjusted hazard ratio (HR) from the counterfactual dataset and inverse probability weights.

Selecting the preferred PSM application

We applied 9 different matching algorithms. We assessed performance to identify our preferred matching method in the context of the data, in the following ways:

- Compared time to event for PPLL extension group with time to event in the matched CLARITY LL group – HR closer to 1 was preferred
- Compared standardised differences – smallest difference between samples was preferred
- Number of unmatched observations – fewest unmatched preferred
- Maximum weighting – smallest preferred

References

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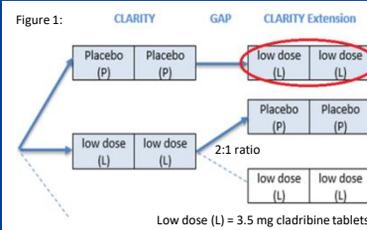


Table 1: Number of patients in CLARITY and CLARITY extension

Treatment	Clarity	Clarity Extension
PPLL	437	244
LLPP	433	98
LLLL		186

Included covariates

age, sex, region, time since first attack, prior use of any disease modifying drugs, expanded disability status scale (EDSS), T1 Gd-enhanced volume, T1 Hypointense Lesions volume, T2 Lesions volume, binary indicator of the number of T1 Gd-enhancing Lesions (1 if 10 or more, and 0 if otherwise), binary indicator of the number of T1 Hypointense Lesions (1 if 10 or more, and 0 if otherwise)

Table 2: Results from adjusted and unadjusted analyses

	HR		
	Point estimate	Lower 95% CI	Upper 95% CI
Time to 3-month confirmed disability progression			
CLARITY ITT (LLvsPP)	0.60	0.41	0.87
RPSFTM (LLPPvsPPPP)	0.62	0.46	0.84
PS 1-to-1 NN with replacement (caliper 0.01) (LLPPvsPPPP)	0.60	0.44	0.83
PS 1-to-1 NN with replacement (caliper 0.01) +IPCW (LLPPvsPPPP)	0.61	0.43	0.86
Time to 6-month confirmed disability progression			
CLARITY ITT (LLvsPP)	0.58	0.40	0.83
RPSFTM (LLPPvsPPPP)	0.62	0.44	0.88
PS kernel matched adjusted (LLPPvsPPPP)	0.62	0.40	0.84
PS kernel matched adjusted +IPCW (LLPPvsPPPP)	0.63	0.40	0.87
Time to First qualifying relapse			
CLARITY ITT (LLvsPP)	0.44	0.34	0.58
RPSFTM (LLPPvsPPPP)	0.48	0.36	0.62
PS kernel matched adjusted (LLPPvsPPPP)	0.48	0.37	0.63
PS kernel matched adjusted +IPCW (LLPPvsPPPP)	0.47	0.38	0.63

RPSFTM - Rank preserving structural Failure time model using g-estimation, PS - propensity score, IPCW - inverse probability of censoring weights
ITT - intention to treat (unadjusted analyses), ITT HRs estimated using cox - proportional hazard models, all analyses control for region

Results

The adjusted (LLPP vs PPPP) HR results of our preferred RPSFTM, PSM and PSM+IPCW analyses are presented in table 2 for time to 3 month confirmed disease progression (CDP), 6 month CDP and first qualifying relapse. Unadjusted HRs are presented for CLARITY ITT (LL vs PP).

Conclusion

We introduced an alternative treatment switching adjustment method, which is relevant in the context of a trial plus extension trial where control group patients switch treatment at the beginning of the extension study. The results from the PSM and PSM+IPCW adjustment methods results are similar to the RPSFTM results, thus providing increased confidence in the validity of the RPSFTM results. The results show no statistical evidence of waning of the 3.5 mg/kg (low-dose) cladribine treatment effect during the Extension study. Furthermore, the similarity in the PSM+IPCW HRs and PSM/RPSFTM HRs indicates the results are not substantially affected by bias from informative drop-out, assuming that all relevant patient characteristics were observed and incorporated in our PSM+IPCW model.