ADJUSTING FOR TREATMENT SWITCHING IN THE RELAPSE-REMITTING MULTIPLE SCLEROSIS CLARITY TRIAL AND CLARITY EXTENSION

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Objectives

Treatment switching adjustment methods are often used to adjust for switching from the control group treatment to the intervention treatment in oncology trials.[1] We applied statistical methods to adjust for treatment switching from placebo to low-dose cladribine tablets in the context of the CLARITY multiple sclerosis trial followed by the CLARITY Extension study. Patients that received placebo in CLARITY switched to 3.5mg (low-dose) cladribine in the extension study. In the absence of an observed placebo arm in both parts of the trial, our analysis aimed to estimate the treatment effect of receiving low-dose cladribine in CLARITY followed by placebo in extension compared with placebo for the duration of the trial and extension (LLPP vs PPPP).

CLARITY and Extension trial design

• The Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) trial and subsequent extension study aimed to evaluate the efficacy of cladribine tablets compared with placebo in relapse-remitting multiple sclerosis patients.
• In CLARITY, patients were randomised 1:1:1 to compare placebo, 3.5 mg (low-dose) cladribine and 5.25 mg (high-dose) cladribine over a 96 week study period.
• Following the CLARITY study, there was a gap period. The median gap time was approximately 40 weeks.
• After the gap period, the CLARITY study went into an 96-week extension trial with a 24-week supplemental follow-up phase.
• Placebo group patients that enrolled in the extension study received low dose cladribine. Low dose cladribine group patients that enrolled in the extension were randomised to receive placebo or low dose cladribine.
• Figure 1 illustrates the treatment pathways for patients randomised to receive placebo or low-dose cladribine in CLARITY.

Treatment switching adjustment methods

Two-stage method[2] and inverse probability of censoring weights (IPCW):[3]
• Require a proportion of non-switching control group patients
  Based on the absence of data on non-switching placebo group patients, it is not possible to apply the two-stage method or the IPCW to adjust for treatment switching in CLARITY and CLARITY extension.

Rank preserving structural failure time model (RPSFTM) (g-estimation/IPE algorithm):[4,5]
• Can be applied in situations where all control group patients switch treatment because it is based on treatment duration
• Require a common treatment effect assumption –
  The treatment effect received by patients in the PPLL arm is the same as the treatment effect received by those in the LLPP arm, relative to the time treatment is taken for.
• Require a randomisation assumption –
  The characteristics of patients are balanced in each arm of the trial

Results

Table 2 shows hazard ratios (HRs) for time to 3-month, 6-month confirmed disability progression and first qualifying relapse end points, for:
  - ITT: LLPP vs PPLL based on combined CLARITY and extension study periods
  - CLARITY ITT: LL vs PP based only on CLARITY
  - RPSFTM: LLPP vs PPPP using RPSFTM adjustment
  - IPE: LLPP vs PPPP using IPE adjustment
• HRs produced by RPSFTM and IPE are consistent.
• The counterfactual HRs are close to 1 indicating that the methods performed well. The RPSFTM consistently performed better than the IPE.
• We performed further analyses to test sensitivity of the results to the common treatment effect assumption, by repeating the RPSFTM with a 20% reduced/increased treatment effect in the PPLL arm. The results remained consistent - HRs within 0.01 of the original result.
• The comparison of the CLARITY ITT HRs with the adjusted HRs indicates that there is no statistical evidence of the low-dose cladribine treatment effect waning over the subsequent 96-week placebo period .
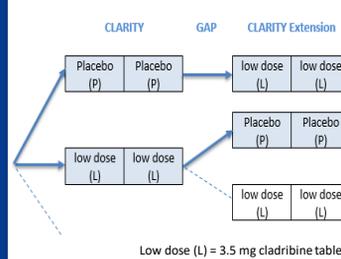
Figure 1: CLARITY and CLARITY Extension

Low dose (L) = 3.5 mg cladribine tablets

Table 1: Number of patients in CLARITY and CLARITY extension

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

Table 2: Results from adjusted and unadjusted analyses

	Hazard Ratio (HR)			CF HR test
	Point estimate	Lower 95% CI	Upper 95% CI	
Time to 3-month confirmed disability progression				
ITT (LLPP vs PPLL)	0.67	0.52	0.87	-
CLARITY ITT (LL vs PP)	0.60	0.41	0.87	-
RPSFTM (LLPP vs PPPP)	0.62	0.46	0.84	1.00
IPE (LLPP vs PPPP)	0.62	0.45	0.83	0.94
Time to 6-month confirmed disability progression				
ITT (LLPPvsPPLL)	0.67	0.50	0.90	-
CLARITY ITT (LL vs PP)	0.58	0.40	0.83	-
RPSFTM (LLPP vs PPPP)	0.62	0.44	0.88	1.01
IPE (LLPP vs PPPP)	0.62	0.43	0.87	0.98
Time to First qualifying relapse				
ITT (LLPPvsPPLL)	0.53	0.43	0.67	-
CLARITY ITT (LL vs PP)	0.44	0.34	0.58	-
RPSFTM (LLPP vs PPPP)	0.48	0.36	0.62	1.00
IPE (LLPP vs PPPP)	0.48	0.37	0.62	0.95

RPSFTM - Rank preserving structural Failure time model using g-estimation, IPE – RPSFTM using the Iterative parameter estimation algorithm, ITT – intention to treat (unadjusted analyses) , ITT HRs estimated using cox –proportional hazard models, all analyses control for region

Limitations

• Not all patients in CLARITY entered into the extension study, therefore the randomisation assumption will not hold if drop-out is related to prognosis, treatment received or capacity to benefit. This limitation is addressed in an additional analysis.[6]
• No long-term data on non-switchers - results must be interpreted with caution.

Conclusions

• It is possible to apply the RPSFTM in the context of a trial plus an extension trial. The analyses appear to have functioned appropriately and results are reassuringly consistent across the different adjustment methods.
• The results do not appear to be sensitive to violations in the common treatment effect assumption.
• There is no statistical evidence to suggest that the treatment benefit of 3.5 mg (low-dose) cladribine waned over the subsequent 96-weeks of the extension study, where patients received placebo.

References

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