Causal inference tools for estimating the effect of beta-interferon exposure in delaying disease progression in relapsing-remitting multiple sclerosis patients: an observational study

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1. Objective

Longitudinal observational data are required to assess the association between beta-interferon (β-IFN) drug exposure and disease progression in relapsing-remitting multiple sclerosis (MS) patients. Marginal Structural Cox Model (MSCM) represents a causal inference survival analysis tool for analyzing longitudinal observational study that allows adjustment for baseline characteristics as well as time-varying confounders through the use of inverse probability treatment and censoring (IPTC) weighting, a function of propensity scores in longitudinal settings. (2) We investigated this association in ‘real-world’ settings using a novel MSCM approach (3).

2. Causal Diagram

According to the causal diagram (1) shown in Figure 1, in the first time period, cumulative relapse in the last two years (R_j) imposes confounding for the treatment exposure (E_j) and disease outcome (D_j) relationship, but cumulative relapse in the next time period (R_{j+1}) is the intermediate variable for the same relationship.

Therefore, cumulative relapse in the last two years is a time-varying confounder. Simply incorporating such time-varying confounder as baseline or time-dependent covariate in a time-dependent Cox model may be inadequate for adjustment for selection bias and confounding (2). Use of IPTC weighting, a function of propensity scores in longitudinal settings (2). We investigated this well as time-varying confounders through the use of inverse probability treatment and censoring (IPTC) weighting, a function of propensity scores in longitudinal settings (2). We investigated this well as time-varying confounders through the use of inverse probability treatment and censoring (IPTC) weighting, a function of propensity scores in longitudinal settings (2). We investigated this well as time-varying confounders through the use of inverse probability treatment and censoring (IPTC) weighting, a function of propensity scores in longitudinal settings (2). We investigated this well as time-varying confounders through the use of inverse probability treatment and censoring (IPTC) weighting, a function of propensity scores in longitudinal settings (2). We investigated this well as time-varying confounders through the use of inverse probability treatment and censoring (IPTC) weighting, a function of propensity scores in longitudinal settings (2). We investigated this well as time-varying confounders through the use of inverse probability treatment and censoring (IPTC) weighting, a function of propensity scores in longitudinal settings (2).

3. Methodology

• A retrospective study of prospectively collected data (1995-2008) in British Columbia (4)
• Baseline was considered as the first date a patient became eligible for β-IFN treatment between July 1995 and Dec 2004. The mean follow-up time was 4 years (IQR 4.3 years).
• The survival outcome measure was time from β-IFN treatment eligibility to a sustained EDSS 6.

To fit a MSCM, we need to choose appropriate IPTC weights from the list below (3):

1. unstabilized weights w
2. unstabilized normalized weights w_{st}(n)
3. stabilized weights w_{st}
4. stabilized normalized weights w_{st}(n)

4. Choosing Appropriate Weights

To find suitable weights for this chronic disease setting, we assess the statistical criteria of the weights (mean weight close to 1 and smaller variance) in Figure 2. w_{st}(n) meets these criteria.

5. Main Results

Using MSCM (with w_{st}(n)) we adjust for potential baseline confounders, including age, sex, disease duration, EDSS score, and time-varying potential confounders (i.e., MS relapses). From this model, exposure to β-IFN was not associated with a statistically significant difference in the hazard of reaching EDSS 6 (hazard ratio: 1.36; 95% CI: 0.95-1.94 from Table 2).

6. Conclusion

Using a novel statistical approach that allows adjustment for potential indication bias and related changes in patient characteristics which might influence subsequent treatment decisions, association between β-IFN exposure and the hazard of disability progression was not found to be significant among patients with relapsing-remitting MS in the ‘real-world’ clinical practice setting.

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Selected References


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