

Supplemental Data

eMethods

Statistical analysis – Cox regression model structure

Given the real-world nature of our study, the treatment schedule in our cohort was very heterogeneous, especially when new guidelines were implemented in different moments of patients' follow up time. Therefore, in order to more precisely model the efficacy of a treatment that is administered periodically with variable treatment intervals throughout time on treatment, we designed the statistical analysis in order to investigate separately every treatment interval, instead of patients. In order to account for dependence of observations deriving from analyzing multiple treatment intervals from the same patient we used a sandwich estimator for the standard errors.

We then used Cox proportional hazard regression models setting the underlying time scale as time since disease onset, in order to compare treatment episodes at the same point along disease history. Subsequently, we specified that study entry coincided with every treatment episode, with start at time of infusion and censoring at the next infusion. In other words we used the "counting process" or (start, stop] set-up for the Cox regression and each time-at-risk window was left truncated, thus avoiding immortal time bias. Re-inclusion of the patient for a subsequent infusion did not restart the clock at time zero but was regarded as a new delayed entry at the infusion date on the original time scale (date of disease onset)^{e1}.

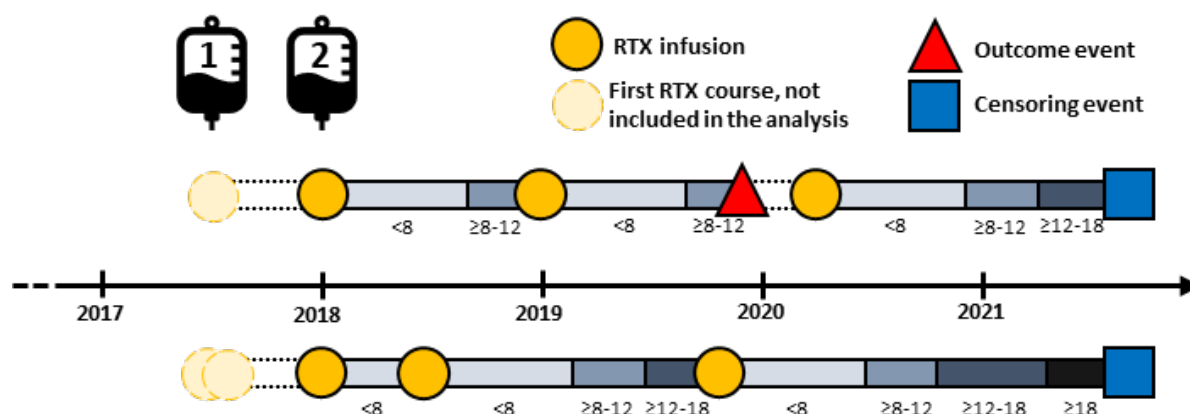
Then, since exposure categorization according to the duration of the treatment interval would have been problematic for the retrospective nature of this allocation, we decided not to bin treatment intervals, but time since last rituximab dose. The four time bands considered were <8, ≥8 to 12, ≥12 to 18 and ≥18 months. Accordingly, in case of an extended treatment interval, such interval did not contribute only to the longest interval category, but was split into the aforementioned time bins (also

in this case taking advantage of the counting process), thus configuring treatment interval as a time-dependent covariate^{e2}.

For example, if a treatment interval lasted 15 months until censoring/outcome event, this contributed to three time intervals, i.e. the <8 months group, the ≥8-12 months group and finally also the ≥12-18 group with the remaining 3 months. In this scenario, in case of relapse after 15 months, disease activity was attributed only to the longest interval, but not to the <8 and ≥8-12 months bins.

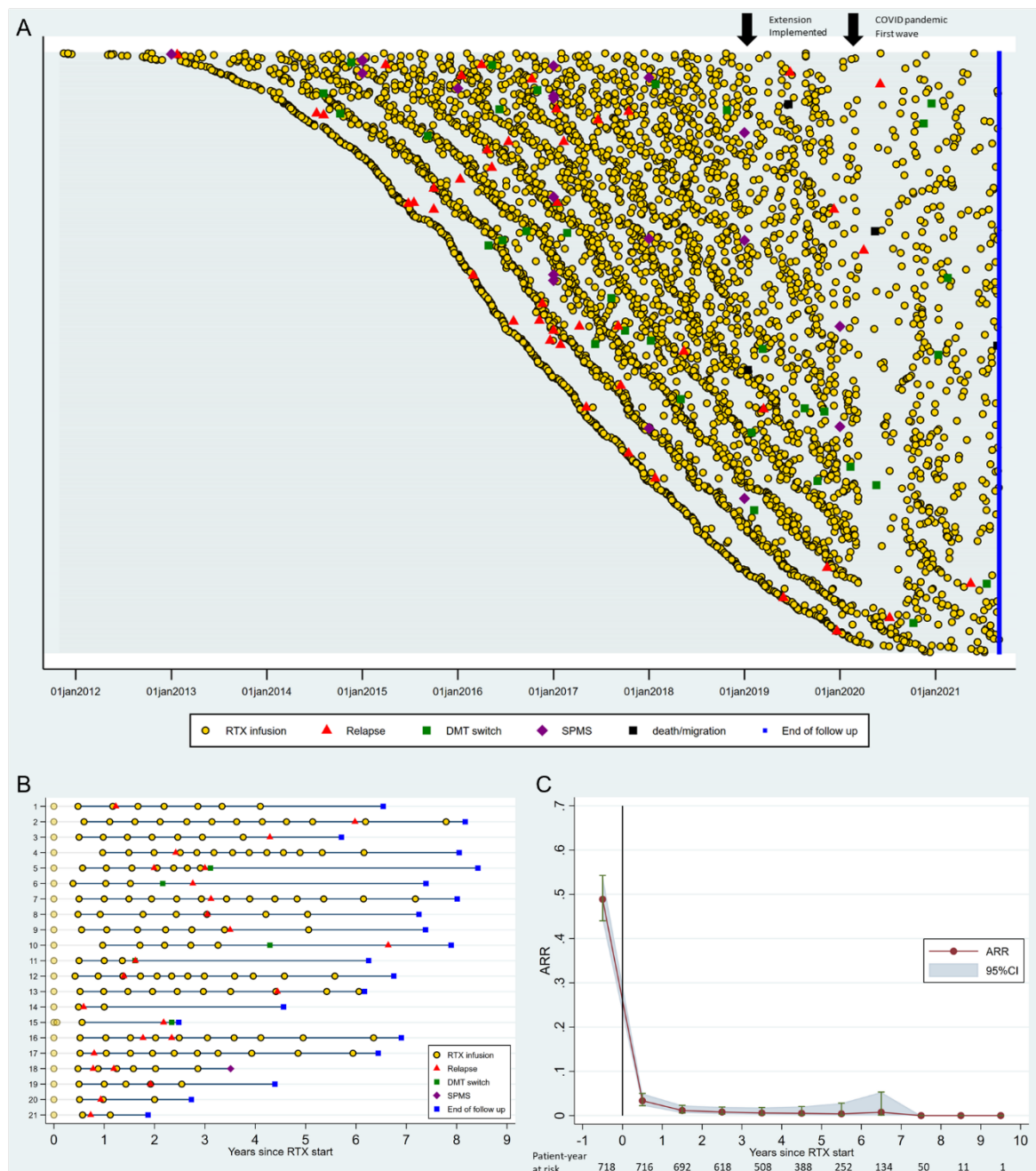
A sketch of the analysis structure is provided in eFigure 1.

eFigure 1



Treatment interval analysis. Two hypothetical patients are depicted from start of rituximab treatment. The time after the first treatment course is excluded from the analysis. Subsequently, the patient enters the study at every drug infusion and time since last rituximab dose is binned in four time bands: <8, ≥8 to 12, ≥12 to 18 and ≥18 months. RTX, rituximab.

eFigure 2



Study cohort overview and clinical relapses. Panel A: overview of the study cohort, with lines representing individual patients and symbols indicating rituximab infusions, clinical relapses and censoring events, as per legend. Panel B: overview of relapses occurring after the second treatment course of rituximab in relation to infusion history. The first treatment interval, transparent, has been excluded from the analysis. Panel C: annualized relapse rate in relation to rituximab start. ARR, annualized relapse ratio; CI, confidence interval; DMT, disease modifying therapies; RTX, rituximab; SPMS, secondary progressive multiple sclerosis.

eReferences

- e1. Therneau TM, Grambsch PM. *Modeling survival data : extending the Cox model*. Statistics for biology and health. xiii, 350 s.
- e2. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med*. Apr 2018;6(7):121. doi:10.21037/atm.2018.02.12