Title page

Title: Starting high-efficacy therapy early minimises long-term disability in multiple sclerosis

Authors:

Anna He, MBBS; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia;

Bernd Merkel, PhD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia

James William Lyle Brown, MD; Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK; NMR Research Unit, Queen Square Multiple Sclerosis Centre, University College London, Institute of Neurology, London, UK; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia

Lana Zhovits, MD; New York University Langone Medical Centre, New York, USA

Ilya Kister, MD; New York University Langone Medical Centre, New York, USA

Charles B Malpas, PhD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia

Sifat Sharmin, PhD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia

Dana Horakova, MD, Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic

Eva Kubala Havrdova, MD, Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic

Tim Spelman, PhD; Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

Guillermo Izquierdo, MD; Hospital Universitario Virgen Macarena, Sevilla, Spain

Sara Eichau, MD; Hospital Universitario Virgen Macarena, Sevilla, Spain

Maria Trojano, MD; Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari, Bari, Italy

Alessandra Lugaresi, MD, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; Department of Biomedical and Neuromotor Science, University of Bologna, Bologna, Italy

Raymond Hupperts, MD, Zuyderland Ziekenhuis, Sittard, Netherlands

Patrizia Sola, MD, Department of Neuroscience, Azienda Ospedaliera Universitaria, Modena, Italy

Diana Ferraro, MD, Department of Neuroscience, Azienda Ospedaliera Universitaria, Modena, Italy

Jan Lycke, PhD, Department of Clinical Neuroscience, Institute of Neuroscience and Physiology at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Francois Grand'Maison, MD; Neuro Rive-Sud, Quebec, Canada

Alexandre Prat, MD; Hopital Notre Dame, Montreal, Canada; CHUM and Universite de Montreal, Montreal, Canada

Marc Girard, MD; Hopital Notre Dame, Montreal, Canada; CHUM and Universite de Montreal, Montreal, Canada

Pierre Duquette, MD; Hopital Notre Dame, Montreal, Canada; CHUM and Universite de Montreal, Montreal, Canada

Catherine Larochelle, MD; Hopital Notre Dame, Montreal, Canada; CHUM and Universite de Montreal, Montreal, Canada

Anders Svenningsson, MD Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden

Thor Petersen, MD; Kommunehospitalet, Arhus C, Denmark

Pierre Grammond, MD; CISSS Chaudière-Appalache, Levis, Canada

Franco Granella, MD; Department of Medicine and Surgery, University of Parma, Parma, Italy

Vincent Van Pesch, MD; Cliniques Universitaires Saint-Luc, Brussels, Belgium; Université Catholique de Louvain

Roberto Bergamaschi, MD; IRCCS Mondino Foundation, Pavia, Italy

Christopher McGuigan, MD; School of Medicine and Medical Sciences, University College Dublin, and St Vincent's University Hospital, Dublin, Ireland

Alasdair Coles, PhD; Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom

Jan Hillert, MD; Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Fredrik Piehl, MD; Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Helmut Butzkueven, PhD; Central Clinical School, Monash University, Melbourne, Australia; Department of Neurology, The Alfred Hospital, Melbourne, Australia; Department of Neurology, Box Hill Hospital, Monash University, Melbourne, Australia

Tomas Kalincik, PhD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia; Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia

on behalf of the MSBase study group

(the list of MSBase contributors is provided in Supplementary appendix S1)

Corresponding Author

Tomas Kalincik,

L4 East, CORe, Royal Melbourne Hospital,

300 Grattan St, Parkville, VIC 3050, Australia

Tel: +61 3 9342 4404

Fax: +61 3 9349 5997

Email: tomas.kalincik@unimelb.edu.au

Word count, manuscript: 2922

Word count, abstract: 300

References: 30

Figures: 3

Tables: 2

Key words: relapsing-remitting multiple sclerosis; disease modifying therapy; relapses; disability; personalised therapy

Abbreviations

EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; ROMAN, rituximab, ocrelizumab, mitoxantrone, alemtuzumab, and natalizumab.

Abstract

Background

It remains unclear whether early commencement of high-efficacy therapies (rituximab, ocrelizumab, mitoxantrone, alemtuzumab, natalizumab; ROMAN) is associated with less long-term disability than the traditional approach of escalation after failure of first-line therapies in multiple sclerosis.

Methods

Using international multiple sclerosis registries, we propensity-score matched patients with relapsing-remitting multiple sclerosis who commenced ROMAN therapies within 0-2 years (early), or between 4-6 years (late) from clinical disease onset. Outcomes were assessed 6-10 years after disease onset. The primary outcome, Expanded Disability Status Score (EDSS, 0-10, higher scores indicate greater disability), was evaluated with a linear mixed effects model. Secondary outcomes - the cumulative hazards of (i) confirmed disability progression and (ii) treatment discontinuation - were analysed with proportional hazards models.

Findings

Among eligible patients treated with ROMAN therapy, 277 patients commenced early and 267 commenced late. For the primary analysis, 213 patients in the early group were matched to 253 in the late group. At baseline, the mean (SD) EDSS was 2·2 (1·2) and 2·1 (1·2) in early vs late groups, respectively. Median (IQR) follow-up time was 7·8 (6·7-8·9) years. In the sixth year, the EDSS was 2·2 (1·6) in the early group compared to 2·9 (1·8) in the late group ($p<0·001$). This difference persisted throughout each year of follow-up until the tenth year (EDSS 2·3 (1·8) vs 3·5 (2·1); $p<0·001$).

Interpretation

Commencing ROMAN therapy within two years of disease onset is associated with less disability in 6-10 years compared to commencing later. This informs decisions regarding optimal sequence and timing of multiple sclerosis therapy.

Funding

This study was funded by NHMRC Australia [1129189, 1140766] and MS Society UK [award #46]. MSBase is a not-for-profit organization, supported by Roche, Merck, Biogen, Novartis, Bayer-Schering, Sanofi-Genzyme, and Teva. The Swedish MS registry is a national health care registry, supported by the Swedish Association of Local Authorities and Regions.

Article

Introduction

Multiple sclerosis is the leading non-traumatic cause of neurological disability in the young.[1] The most commonly used paradigm for treatment of relapsing-remitting multiple sclerosis, endorsed by many regulatory bodies, is 'treatment escalation'. According to this paradigm, patients first commence a low-risk, moderate-efficacy immunotherapy, switching to more efficacious therapies (with more serious side-effect profiles) if breakthrough disease activity is encountered.[2]

Rituximab[3], ocrelizumab[4], mitoxantrone[5], alemtuzumab[6,7], and natalizumab[6] (here collectively termed 'ROMAN' therapies) confer a greater reduction in relapse rates compared to the traditional first line agents interferon-beta-1a and glatiramer acetate. It is unclear whether early commencement of ROMAN therapies also reduces long-term disability accrual compared to later commencement.

No randomised trials have specifically addressed this question due to, amongst other factors, the cost and logistic aspects of recording long term outcomes, and ethical considerations[8]. High quality longitudinal observational data are valuable in addressing such questions by exploiting the heterogeneity in treatment protocols due to differences in drug licencing and availability across different geographic and historical groups.[9–11]

Here we compare long-term disability outcomes between patients commencing ROMAN therapies within two years of disease onset compared to those commencing ROMAN therapies later (between 4-6 years).

Methods

Study design

This study compared disability outcomes 6-10 years from disease onset between patients commencing ROMAN therapies within 0-2 years of disease onset versus between 4-6 years.

Data sources

The study used observational data from MSBase, a large international multiple sclerosis registry,[9] 61 MSBase centres in 17 countries recorded the studied data as part of routine clinical follow-up between February 1990 to April 2017 using the iMed software or the MSBase online data entry system. Ethical approval was granted by the Melbourne Health Human Research Ethics Committee and by each site's institutional review boards (or exemptions were granted according to local regulations). All patients provided written or verbal informed consent as per local institutional regulations. Additional data derived from the Swedish MS Registry[12]. Although participation is voluntary, coverage is close to 80% of the prevalent Swedish MS population with a very high validity of recorded data on treatment (initiation/duration) and disease activity at treatment start[13]. Ethical approval was granted by the Stockholm County Ethical Review Board and all patients provided verbal informed consent.

Participants

Inclusion criteria were: a diagnosis of clinically definite relapsing-remitting multiple sclerosis,[14,15] minimum age of 18 years at time of diagnosis, minimum six consecutive months of treatment with at least one ROMAN therapy, minimum follow-up time of six years since first symptom (considered the time of clinical disease onset) with at least six months follow-up since commencement of ROMAN, and availability of a minimum baseline dataset (date of birth, sex, treating centre, date of disease onset, date of confirmation of clinically definite multiple sclerosis, availability of dates of clinical relapses, and availability of at least one disability score recorded within the first two years after disease onset and one disability score, not related to a relapse, recorded at six years or later). For analyses where confirmed progression of disability was the studied outcome (see below), at least two

recorded disability scores at least six months apart were required after commencing the ROMAN therapy.

The early treatment group was defined as patients first commencing ROMAN within two years of disease onset. The late treatment group was defined as patients first commencing ROMAN therapy 4-6 years after disease onset (with at least six months on treatment at the specified follow-up time). Patients in both groups could be pre-treated with any non-ROMAN therapy prior to ROMAN commencement. Patients treated with haemopoietic stem cell transplant were excluded.

Procedures

ROMAN therapies were administered according to published protocols:

1. Rituximab (one, or two doses two weeks apart of 500mg-1g intravenously , followed by 1-2 doses of 500mg-1g, at 6-12-month intervals thereafter)[3]
2. Ocrelizumab, 600mg intravenously, every 24 weeks[4]
3. Mitoxantrone, 12mg per square meter body surface area intravenously, every three months, or equivalent[5]
4. Alemtuzumab, 12-24mg intravenously, daily for five days (cycle 1) then daily for three days (all subsequent cycles)[7]
5. Natalizumab, 300mg intravenously, every four weeks[16]

Other disease-modifying therapies, including ß-interferon, glatiramer acetate, and oral therapies (fingolimod, teriflunomide, dimethyl fumarate, cladribine), were not classified as high-efficacy on the basis of comparative studies to the ROMAN therapies.[6]

Duration of treatment effect was assumed as the lowest estimated duration of biological effectiveness: six months for rituximab, ocrelizumab, and mitoxantrone; five years for alemtuzumab; two months for natalizumab.

Outcome measures

The primary endpoint was disability, as measured by the Expanded Disability Status Scale (EDSS)[17]

during years six to 10 after disease onset. The EDSS is an ordinal scale (range 0-10, based on clinical examination), graded in steps of 0·5, with larger values representing greater disability. The secondary outcome measures were (i) confirmed disability progression events - defined as an increase in EDSS by one step (1·5 steps if baseline EDSS was 0 and 0·5 steps if baseline EDSS was >5·5) confirmed by equal or higher EDSS scores over at least six months;[18] and (ii) discontinuation of the first ROMAN therapy.

Statistical methods

Statistical analyses were performed using R version 3·4·3.[19] To minimise indication bias, patients included in each analysis were selected by matching their individual propensity of commencing ROMAN therapies early (versus late), conditional on their demographic and clinical variables in the first two years of their disease. The following variables were fitted to a logistic regression model to derive the propensity score: patient age at disease onset, sex, the number of relapses during the 12 months preceding commencement of first immunotherapy (or between year 1-2 of the baseline period, whichever occurred earlier), delay from first symptom to clinically definite MS, and median EDSS during the two year baseline period. Patients were matched on propensity score using nearest neighbour matching without replacement, calliper of 0·1, and variable matching ratio of 1:5. Comparison of baseline variables between groups was performed using standardised mean difference, where <0·20 was considered acceptable balance. For each analysis, the propensity score matching procedure used only patients for whom outcome data were available during the relevant follow-up period of the analysis. All analyses were weighted to account for the variable matching ratio, with the maximum cumulative weight for each matched patient being 1.

The association between early versus late commencement of ROMAN therapies on EDSS over the follow-up period (years 6-10 from disease onset) was modelled using a linear mixed effects model. Treatment group, proportion of time on any disease-modifying immunotherapy, and disease duration were modelled as fixed effects; patient identifier and pair identifier were modelled as random intercepts to account for interdependence of repeated measures from each patient and the matched

nature of the data, respectively. EDSS scores during each individual year between years 6-10 were compared using linear regression models, also including proportion of time on any immunotherapy as a covariate, with separate matching was carried out for each analysed year epoch. Median EDSS at a given year was calculated for each patient. A clinically significant treatment effect was prespecified as ≥0·5 EDSS steps. Sensitivity analyses were performed by including proportion of time on immunotherapy, and time from disease onset to first disease-modifying treatment, as a covariate in the primary models (to adjust for potential systematic differences in total time spent on any immunotherapy, and time to commencing any immunotherapy, respectively), and by repeating the analysis with EDSS as an ordinal variable using ordinal regression (to account for the nonlinear nature of the EDSS).

The following secondary analyses were performed. Cumulative hazard of confirmed disability progression events was modelled with three Andersen-Gill proportional hazards models using three different landmarks as the baseline for the analysis: time of disease onset; time of initiation of first disease-modifying therapy; and six years after disease onset. Cumulative time on any disease-modifying immunotherapy was included as an independent predictor. The probability of discontinuation of ROMAN therapy was estimated using a Cox proportional hazards model, with the baseline being the time of ROMAN commencement. Proportionality of hazards was examined with Schoenfeld residuals. Results were considered statistically significant at the $p < 0{\cdot}05$ level.

Role of the funding source

This study was conducted separately and apart from the guidance of the funding source.

Results

Participants

Among the screened records, we identified 6149 patients in the MSBase registry and 2626 in the Swedish Multiple Sclerosis Registry exposed to ROMAN therapies. Of these, 307 patients (131 in the early group, 177 in the late group) in the MSBase registry and 237 patients (146 in the early group, 90 in the late group) in the Swedish MS Registry fulfilled the inclusion criteria and had complete baseline and follow-up data available for further analysis (Figure 1). Country of treatment is available in Supplementary Appendix S2.

For the primary analysis, 213 patients in the early group were matched with 253 patients in the late group (see Supplementary Appendix S3 for the regression model and outcomes of matching). The characteristics of eligible patients before and after matching are listed in Table 1. The two matched groups were well balanced on the measured characteristics during the baseline period (standardised difference <0·20). Patients in the early group commenced their first immunotherapy earlier than those in the late group (mean (SD) 218 (169) days versus 415 (419) days, respectively), and had longer total time on immunotherapy during years 0-10 (mean (SD) 6·35 (1·83) vs 5·20 (2·05) years in early vs late groups, respectively; pairwise right-censored) as well as longer time on ROMAN therapy (4·89 (2·33) vs 2·41 (1·40) years, respectively). Proportion of patients treated with each ROMAN therapy is given in Supplementary Appendix S4.

Primary analysis: disability in years 6-10 from disease onset

The primary outcome was the difference in EDSS during the follow-up period (6-10 years after disease onset) between patients who commenced ROMAN early versus late. The median (IQR) number of EDSS scores recorded per patient was 5 (2-10). The early treatment group had a lower overall EDSS score throughout years 6-10. The adjusted mean difference in EDSS score between groups was -0·98 steps (95%CI -1·51, -0·45. p<0·001), which changed minimally throughout the follow-up (beta for treatment group by time interaction 0·06, 95%CI 0·01, 0·12, p = 0·033, see Figure 2). Proportion of time on any immunotherapy was not predictive of disability (beta = -0·26, 95%CI -0·74-0·22, p=0·295). When the model was adjusted for country of treatment and the specific

ROMAN therapy, the effect of the timing of ROMAN has remained largely unchanged (beta -0·80; 95% CI -1·30, -0·31; p=0·001).

The baseline characteristics and EDSS trajectories of patients not included in the matched cohort are presented in Supplementary Appendix S5.

Comparing disability at each follow-up year, difference in EDSS between groups remained >0·5 each year (Supplementary Appendix S6 shows year-by-year EDSS scores between years 0-5, baseline characteristics of matched cohorts for each year are shown in Supplementary Appendix S7). Mean EDSS was lower in the early group by 0·75 steps (95%CI 0·44-1·05; adjusted beta -0·93 [95% CI -0·60, -1·25], p<0·001) at year 6-7, 0·86 steps (95%CI 0·51-1·22; adjusted beta -0·96 [95% CI -0·59, -1·34], p<0·001) at year 7-8, 0·82 steps (95%CI 0·43-1·22; adjusted beta -0·83 [95% CI -0·41, -1·25], p<0·001) at year 8-9, and 1·19 steps (95%CI 0·74-1·65; adjusted beta -1·30 [95% CI -0·82, -1·78], p<0·001) at year 9-10. Sensitivity analyses, which restricted commencement of first disease-modifying therapy to maximum of two years from disease onset, and modelled EDSS as an ordinal variable, replicated the findings of the primary analysis in full (Odds ratio (95%CI) of moving to a higher EDSS rank during year 6-10 for early vs late group: 0·42 (0·36, 0·50) p<0·001, full results in Supplementary Appendix S8).

Secondary analysis: cumulative hazard of disability progression

Patients commencing ROMAN therapy early had a lower hazard of confirmed disability progression compared to those commencing late. This was seen when cumulative hazards were compared from the date of starting first disease-modifying therapy (HR=0·34, 95%CI 0·23-0·51, p<0·001, Figure 3A) or when compared from the date of disease onset (HR=0·46, 95%CI 0·31-0·68, p<0·001, Figure 3B). It should be noted that in the latter model the estimated hazards were not proportional (rho=-0·3, χ^2=73·4, p<0·001, see Supplementary Appendix S9).

Cumulative hazard of disability progression continued to be lower in the early group from year six onwards, after both groups have been treated with ROMAN therapy (HR=0·38, 95%CI 0·17-0·81, p=0·013, Figure 3C).

Treatment persistence

Patients had similar probability of ROMAN discontinuation regardless of start time (Figure 3D). After discontinuation of ROMAN therapies, 70 (32·8%) patients in the early group switched to another ROMAN compared to 39 (15·6%) patients in the late group (see Table 2). Patients switching from natalizumab as their first ROMAN therapy most commonly de-escalated to oral therapy, those switching from mitoxantrone most commonly de-escalated to injectable therapies.

Discussion

In this observational, propensity score-matched study of disability outcomes among patients with relapsing-remitting multiple sclerosis, commencement of rituximab, ocrelizumab, mitoxantrone, alemtuzumab, or natalizumab (ROMAN therapies) within two years of disease onset was associated with lower long-term absolute disability, as well as lower hazard of disability progression, compared to commencement four to six years after disease onset.

The studied patients were relatively young with active disease, as expected in a cohort commencing potent immunotherapy within six years from disease onset. To study the effect of timing of ROMAN therapy, we predefined two distinct timeframes for the commencement of the ROMAN therapies, separated by two years, as the only systematic difference between groups. Total time on any disease-modifying immunotherapy was found to be systematically longer in the early cohort after matching; this parameter was accounted for as a covariate in all outcome analyses.

The magnitude of disability prevented by earlier treatment was not only statistically but also clinically significant[20], as the EDSS scores in early-starters were on average one step lower than in the late-starters. This difference was sustained throughout years 6-10.

After both groups had been treated with ROMAN therapy at 6 years, cumulative hazard of disability progression continued to diverge in favour of the early group. This may either be due to ROMAN therapies exerting greater efficacy on long-term disability progression when started earlier in the disease compared to later, or due to longer cumulative time on ROMAN therapy. Our study cannot

dissociate the two as early starters spent longer on ROMAN therapy, but this effect was present even with total time on (any) immunotherapy included in the model.

The agents classed as "high-efficacy therapies" have been selected based on comparative studies that demonstrated their superior effectiveness compared to ß-interferon or glatiramer acetate, and oral agents.[4,6,7,16,20,2122] Although timing of high-efficacy therapy has not previously been evaluated directly, other studies have shown that earlier commencement of any immunotherapy, including first-line agents, mitigates relapse activity more effectively than their delayed start[23,24]. Subgroup analyses and open-label extensions of randomised controlled trials suggest that earlier commencement of high-efficacy therapies improves the control of relapse activity, but were unable to evaluate its effect on disability outcomes[8,25,26]. Our present study unifies the two principles of early treatment and higher-efficacy therapy into a conceptual framework for early aggressive immunotherapy in active multiple sclerosis.

The main limitations of the study pertain to the observational nature of the data.[10] We adopted measures to mitigate the impact of the heterogeneity of the data, including assessment of data quality[13,27]. Furthermore, the EDSS outcome metric, while based on clinical examination, has multiple limitations, including its low sensitivity and ordinal nature[17]. Despite this, it is the most widely used disability metric both clinically and in research. The primary outcome was confirmed by sensitivity analyses that used ordinal regression, which is robust in the setting of ordinal scales with unequal step size. Odds ratios of being in a higher EDSS band were consistently <0·5 for the early compared to late groups, during each year of follow-up. Differences in regulatory requirements for use of ROMAN and first-line therapies between countries may represent an additional source of bias; this was detectable in the data as systematic difference in start time of any immunotherapy between the two matched groups as well as difference in total time on immunotherapy. Sensitivity analysis accounting for these detectable differences confirmed the results of the primary analysis in full. We cannot rule out residual indication bias, for example regarding potentially greater disease activity not captured by relapse frequency or initial disability scores for patients starting ROMAN therapies earlier – including

more radiologically active disease in the group of early starters of ROMAN. Importantly, such bias would dilute the reported difference between the studied groups; therefore, the recorded difference of one EDSS step during years 6-10 likely represents a conservative estimate of the benefit with earlier start of high-efficacy immunotherapies. Furthermore, this study was not design to study safety of the two therapeutic approaches, as safety data were not sufficiently complete to enable this analysis.

While high-efficacy therapies achieve more favourable relapse and disability outcomes, not all patients will require aggressive immunotherapy.[21] High-efficacy therapies generally carry more serious adverse event profiles,[20,28] mandating clinical justification for their use and identification of patients most likely to benefit. Such justification may come in the form of a high risk of developing aggressive disease, which is unavoidably associated with high level of disability. Sex, age, and presenting symptoms may predict more disease severity at a group level.[29] With present markers, such as volumetric MRI[30], and emerging markers such as serum neurofilament light chain, early and accurate prognostication in individual patients will become possible.

The present study demonstrates that timing of high-efficacy therapy has a long-term impact on patients' neurological disability; given this, we propose high-efficacy therapy be considered first line for patients with active relapsing-remitting multiple sclerosis. Further research is needed to more accurately identify those patients most likely to benefit from these therapies.

ACKNOWLEDGMENTS

The list of MSBase Study Group co-investigators and contributors is given in Table S1.

Funding

This study was funded by NHMRC Australia [1129189, 1140766] and MS Society UK [award nr. 46]. Cambridge alemtuzumab work was additionally funded by NIHR Cambridge Biomedical Research Centre. MSBase is a not-for-profit organization that receives support from Roche, Merck, Biogen, Novartis, Bayer-Schering, Sanofi-Genzyme, and Teva. The Swedish MS registry is a national health care registry, supported by the Swedish Association of Local Authorities and Regions.

DECLARATION OF INTERESTS

Anna He did not declare any competing interests.

Bernd Merkel did not have any competing interests while involved in this study. He has later become an employee of Biogen.

James William Lyle Brown has received travel expenses, speaker honoraria, and advisory board work from Biogen, Novartis and Sanofi-Genzyme.

Lana Zhovtis Ryerson has served on Speaker Bureau for Teva, Genenzyme, and Biogen; advisory board for Biogen and Celgene; and has received research support from Biogen.

Ilya Kister served on scientific advisory board for Biogen and received research support from Guthy-Jackson Charitable Foundation, National Multiple Sclerosis Society, Biogen, and Novartis.

Charles Malpas did not declare any competing interests.

Sifat Sharmin did not declare any competing interests.

Dana Horakova reports grants from Czech Ministries of Education and Health, during the conduct of the study; personal fees from Biogen Idec, personal fees from Novaetis, personal fees from Sanogi

Genyzme, personal fees from Merck, personal fees from Teva, personal fees from Bayer Schering, outside the submitted work.

Eva Havrdova reports grants, personal fees and non-financial support from Biogen Idec, personal fees and non-financial support from Novartis, personal fees and non-financial support from Genzyme, grants, personal fees and non-financial support from Merck Serono, personal fees and non-financial support from Actelion, personal fees and non-financial support from Celgene, personal fees and non-financial support from Teva, outside the submitted work.

Guillermo Izquierdo reports personal fees from Biogen, Novartis, Sanofi, Merck Serono, and Teva, outside the submitted work.

Sara Eichau received travel grants and/or speaker honoraria from Merck, TEVA, Novartis, Biogen, and Sanofi-Genzyme.

Maria Trojano received speaker honoraria from Biogen-Idec, Bayer-Schering, Sanofi Aventis, Merck, Teva, Novartis, and Almirall; has received research grants for her Institution from Biogen-Idec, Merck, and Novartis.

Alessandra Lugaresi reports grants and personal fees from Bayer, grants and personal fees from Biogen, grants and personal fees from Merck, Serono grants and personal fees from Novartis, personal fees from Roche, grants and personal fees from Sanofi-Genzyme, grants and personal fees from Teva, outside the submitted work.

Raymond Hupperts received honoraria as consultant on scientific advisory boards from Merck, Biogen, Genzyme-Sanofi, and Teva, research funding from Merck and Biogen, and speaker honoraria from Sanofi-Genzyme and Novartis.

Patrizia Sola served on scientific advisory boards for Biogen Idec and TEVA, she has received funding for travel and speaker honoraria from Biogen Idec, Merck, Teva, Sanofi Genzyme, Novartis, and Bayer, and research grants for her Institution from Bayer, Biogen, Merck, Novartis, Sanofi, Teva.

Diana Ferraro received travel grants and/or speaker honoraria from Merck, TEVA, Novartis, Biogen, and Sanofi-Genzyme.

Jan Lycke has received travel support and/or lecture honoraria from Biogen, Novartis, Teva, Merck, and Genzyme/SanofiAventis; has served on scientific advisory boards for Almirall, Teva, Biogen, Novartis, Merck, and Genzyme/SanofiAventis; serves on the editorial board of the Acta Neurologica Scandinavica; and has received unconditional research grants from Biogen, Novartis, and Teva.

Francois Grand'Maison received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, Mitsubishi, and ONO Pharmaceuticals.

Alexandre Prat did not declare any competing interests.

Marc Girard received consulting fees from Teva Canada Innovation, Biogen, Novartis, and Genzyme Sanofi; lecture payments from Teva Canada Innovation, Novartis and EMD. He has also received a research grant from Canadian Institutes of Health Research.

Pierre Duquette served on editorial boards and has been supported to attend meetings by EMD, Biogen, Novartis, Genzyme, and TEVA Neuroscience. He holds grants from the CIHR and the MS Society of Canada and has received funding for investigator-initiated trials from Biogen, Novartis, and Genzyme.

Anders Svenningsson reports no conflicts

Thor Petersen received funding or speaker honoraria from Biogen, Merck, Novartis, Bayer Schering, Sanofi-Aventis, Roche, and Genzyme.

Pierre Grammond is a Merck, Novartis, Teva-neuroscience, Biogen and Genzyme advisory board member, consultant for Merck, received payments for lectures by Merck, Teva-Neuroscience, and Canadian Multiple sclerosis society, and received grants for travel from Teva-Neuroscience and Novartis.

Franco Granella received research grant from Biogen, served on scientific advisory boards for Biogen, Novartis, Merck, and Sanofi-Aventis and received funding for travel and speaker honoraria from Biogen, Merck, Sanofi-Aventis, and Almirall.

Vincent Van Pesch received travel grants from Biogen, Bayer Schering, Genzyme, Merck, Teva, and Novartis Pharma. His institution receives honoraria for consultancy and lectures from Biogen, Bayer Schering, Genzyme, Merck, Roche, Teva, and Novartis Pharma as well as research grants from Novartis Pharma and Bayer Schering.

Roberto Bergamaschi received speaker honoraria from Bayer Schering, Biogen, Genzyme, Merck, Novartis, Sanofi-Aventis, Teva; research grants from Bayer Schering, Biogen, Merck, Novartis, Sanofi-Aventis, Teva; congress and travel/accommodation expense compensations by Almirall, Bayer Schering, Biogen, Genzyme, Merck, Novartis, Sanofi-Aventis, Teva.

Christopher McGuigan has received grants and personal fees from Biogen, Novartis, Genzyme outside the submitted work.

Alasdair Coles reports personal fees and honoraria, consulting fees and travel expenses up until September 2017 for attending meetings from Genzyme, a Sanofi Company, outside the submitted work; in addition, Dr Coles has a patent on the dose regime of alemtuzumab as a treatment of MS pending.

Fredrik Piehl reports research grants from Genzyme, Merck KGaA, and Novartis, and fees for serving as chair of data monitoring committees in clinical trials with Parexel.

Helmut Butzkueven served on scientific advisory boards for Biogen, Novartis, and Sanofi-Aventis, and has received conference travel support from Novartis, Biogen, and Sanofi Aventis. He serves on steering committees for trials conducted by Biogen and Novartis, and has received research support from Merck, Novartis, and Biogen.

Tomas Kalincik reports grants from NHMRC, grants from Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, during the conduct of the study; grants, personal fees and non-

financial support from Biogen, personal fees from Roche, personal fees and non-financial support from Genzyme-Sanofi, personal fees and non-financial support from Merck, personal fees and non-financial support from Novartis, personal fees from WebMD Global, personal fees from Teva, personal fees from BioCSL, outside the submitted work.

References

1 Compston A, Coles A. Multiple sclerosis. 2002; **359**: 1221–31.

2 Fernández O, Delvecchio M, Edan G, *et al.* Survey of diagnostic and treatment practices for multiple sclerosis in Europe. *Eur J Neurol* 2017; **24**: 516–22.

3 Spelman T, Frisell T, Piehl F, Hillert J. Comparative effectiveness of rituximab relative to IFN-β or glatiramer acetate in relapsing-remitting MS from the Swedish MS registry. *Mult Scler J* 2018; **24**: 1087–95.

4 Hauser SL, Bar-Or A, Comi G, *et al.* Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *N Engl J Med* 2017; **376**: 221–34.

5 Edan G, Comi G, Le Page E, *et al.* Mitoxantrone prior to interferon beta-1b in aggressive relapsing multiple sclerosis: a 3-year randomised trial. *J Neurol Neurosurg Psychiatry* 2011; **82**: 1344–50.

6 Kalincik T, Brown JWL, Robertson N, *et al.* Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study. *Lancet Neurol* 2017; **16**: 271–81.

7 Cohen JA, Coles AJ, Arnold DL, *et al.* Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: A randomised controlled phase 3 trial. *Lancet* 2012; **380**: 1819–28.

8 Merkel B, Butzkueven H, Traboulsee AL, Havrdova E, Kalincik T. Timing of high-efficacy

therapy in relapsing-remitting multiple sclerosis: A systematic review. *Autoimmun Rev* 2017; **16**: 658–65.

9 Butzkueven H, Chapman J, Cristiano E, *et al.* MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. *Mult Scler* 2006; **12**: 769–74.

10 Trojano M, Tintore M, Montalban X, *et al.* Treatment decisions in multiple sclerosis-insights from real-world observational studies. *Nat Rev Neurol* 2017; **13**: 105–18.

11 Trojano M, Pellegrini F, Paolicelli D, Fuiani A, Di Renzo V. observational studies: propensity score analysis of non-randomized data. *Int MS J* 2009; **16**: 90–7.

12 Hillert J, Stawiarz L. The Swedish MS registry – clinical support tool and scientific resource. *Acta Neurol Scand* 2015; **132**: 11–9.

13 Alping P, Piehl F, Langer-Gould A, Frisell T, COMBAT-MS Study Group. Validation of the Swedish Multiple Sclerosis Register: Further Improving a Resource for Pharmacoepidemiologic Evaluations. *Epidemiology* 2019; **30**: 230–3.

14 Polman CH, Reingold SC, Edan G, *et al.* Diagnostic criteria for multiple sclerosis: 2005 Revisions to the 'McDonald Criteria'. Ann. Neurol. 2005. DOI:10.1002/ana.20703.

15 Polman CH, Reingold SC, Banwell B, *et al.* Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Ann Neurol* 2011. DOI:10.1002/ana.22366.

16 Rudick RA, Stuart WH, Calabresi PA, *et al.* Natalizumab plus Interferon Beta-1a for Relapsing Multiple Sclerosis. *N Engl J Med* 2006; **354**: 911–23.

17 Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC Neurol* 2014; **14**: 1–10.

18 Kalincik T, Cutter G, Spelman T, *et al.* Defining reliable disability outcomes in multiple sclerosis. *Brain* 2015; **138**: 3287–98.

19 R Development Core Team R. R: A Language and Environment for Statistical Computing. 2011 DOI:10.1007/978-3-540-74686-7.

20 Tramacere I, Del Giovane C, Salanti G, D'Amico R, Pacchetti I, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: A network meta-analysis. *Cochrane Database Syst Rev* 2014; **2014**. DOI:10.1002/14651858.CD011381.

21 Spelman T, Kalincik T, Jokubaitis V, *et al.* Comparative efficacy of first-line natalizumab vs IFN-β or glatiramer acetate in relapsing MS. *Neurol Clin Pract* 2016; **6**: 102–15.

22 Kalincik T, Brown JWL, Robertson N, *et al.* Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study. *Lancet Neurol* 2017; **16**: 271–81.

23 PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. *Neurology* 2001; **56**: 1628–36.

24 Kappos L, O'Connor P, Radue E-W, *et al.* Long-term effects of fingolimod in multiple sclerosis: The randomized FREEDOMS extension trial. *Neurology* 2015; **84**: 1582–91.

25 Coles AJ, Twyman CL, Arnold DL, *et al.* Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet (London, England)* 2012; **380**: 1829–39.

26 Havrdova E, Arnold DL, Cohen JA, *et al.* Alemtuzumab CARE-MS i 5-year follow-up: Durable efficacy in the absence of continuous MS therapy. *Neurology* 2017; **89**: 1107–16.

27 Kalincik T, Kuhle J, Pucci E, *et al.* Data quality evaluation for observational multiple sclerosis registries. *Mult Scler J* 2017. DOI:10.1177/1352458516662728.

28 Luna G, Alping P, Burman J, *et al.* Infection Risks Among Patients With Multiple Sclerosis Treated With Fingolimod, Natalizumab, Rituximab, and Injectable Therapies. *JAMA Neurol* 2019; published online Oct 7. DOI:10.1001/jamaneurol.2019.3365.

29 Menon S, Shirani A, Zhao Y, *et al.* Characterising aggressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2013; **84**: 1192–8.

30 Tintore M, Rovira À, Río J, *et al.* Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain* 2015; **138**: 1863–74.

Figure 1. CONSORT chart of patient disposition

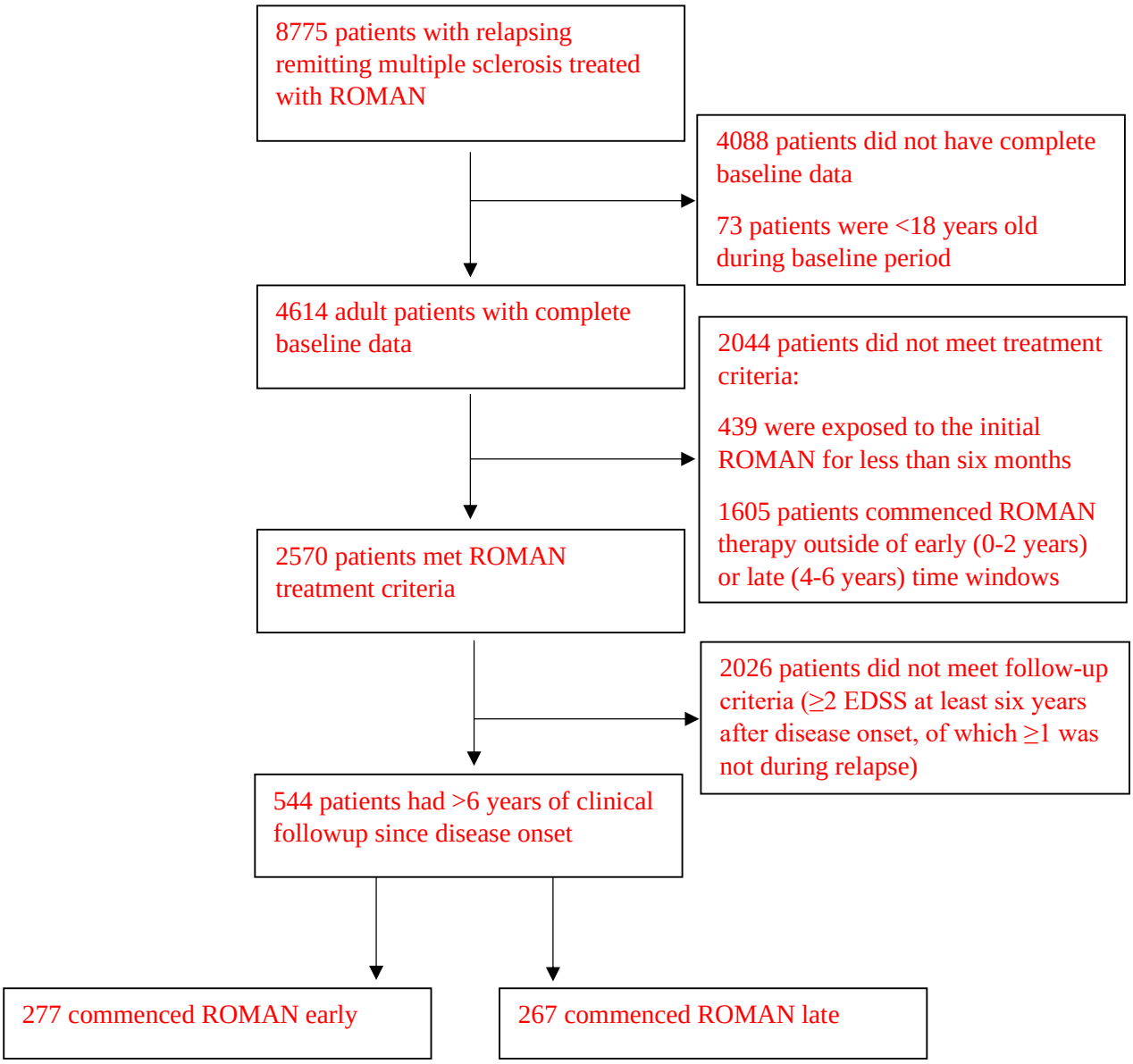


Table 1: Characteristics of eligible patients within first two years of disease onset, before and after matching

All eligible patients	**Early**	**Late**	**Standardised difference**
n	277	267	
Age at disease onset, years (mean (SD))	31·2 (9·2)	30·6 (8·0)	0·06
Males, n (%)	79 (28·5)	72 (27·3)	0·03
Number of relapses in 12 months preceding treatment (mean (SD)) *	1·05 (1·04)	0·95 (0·94)	0·10
Time to clinically definite multiple sclerosis (days, mean (SD))	152 (142)	215 (194)	0·44
EDSS (mean (SD)) #	2·54 (1·40)	1·83 (1·19)	0·51
Time to first ROMAN (years, mean(SD))	1·08 (0·52)	4·99 (0·60)	6·97

Matched patients	**Early**	**Late**	**Standardised mean difference**
n	213	253	
Age at disease onset, years (mean (SD))	30·8 (8·8)	30·8 (7·9)	0·00
Males, n (%)	64 (30·0)	71 (28·1)	0·04
Number of relapses in 12 months preceding treatment (mean (SD))*	0·99 (0·95)	0·99 (0·95)	0·01
Annualised relapse rate in first two years of disease (mean (SD))°	2·36 (1·77)	1·93 (1·51)	0·26
Time to clinically definite multiple sclerosis (days, mean (SD))	165 (152)	161 (144)	0·03
EDSS (mean (SD))#	2·18 (1·20)	2·06 (1·17)	0·08
Time to first ROMAN (years, mean(SD))	1·10 (0·52)	5·01 (0·60)	6·98
First immunotherapy, n (%)			
ß-interferon/glatiramer acetate	65 (30·5%)	184 (72·8%)	
Orals	3 (1·4%)	15 (5·9%)	
Daclizumab	0	1 (0·5%)	
ROMAN	145 (68·1%)	53 (21%)	
First ROMAN therapy			

Anti-CD-20 therapy	14 (7%)	32 (13%)	
Mitoxantrone	32 (15%)	38 (15%)	
Alemtuzumab	1 (0·5%)	3 (1·2%)	
Natalizumab	166 (78%)	182 (72%)	

*Number of relapses in the 12 months immediately preceding start of first immunotherapy or during the second year from MS onset, whichever was earlier. Patients were matched on this criterion.
#Median score 0-2 years after disease onset
°Patients were not matched on this criterion.
EDSS: Expanded disability status scale; ROMAN: rituximab, ocrelizumab, mitoxantrone, alemtuzumab, natalizumab

Table 2: Treatment after initiation of first ROMAN therapy

	Early	Late
Continued ROMAN therapy (n, %)	54 (25·4%)	150 (59·3%)
Another ROMAN therapy (n, %)	70 (32·8%)	39 (15·6%)
Anti-CD-20 therapy	35 (16·4%)	9 (4·1%)
Mitoxantrone	2 (0·9%)	3 (1·4%)
Alemtuzumab	3 (1·4%)	5 (2·2%)
Natalizumab	30 (14·1%)	23 (10·8%)
ß-interferon/glatiramer acetate (n, %)	26 (12·2%)	15 (6·0%)
Oral therapies (n, %)	47 (22·1%)	18 (7·1%)
No treatment after first ROMAN	16 (7·5%)	31 (12·1%)

Figure titles and captions:

Figure 2A: Overall disability trajectories 6-10 years after onset of relapsing-remitting multiple sclerosis treated early versus late with ROMAN.

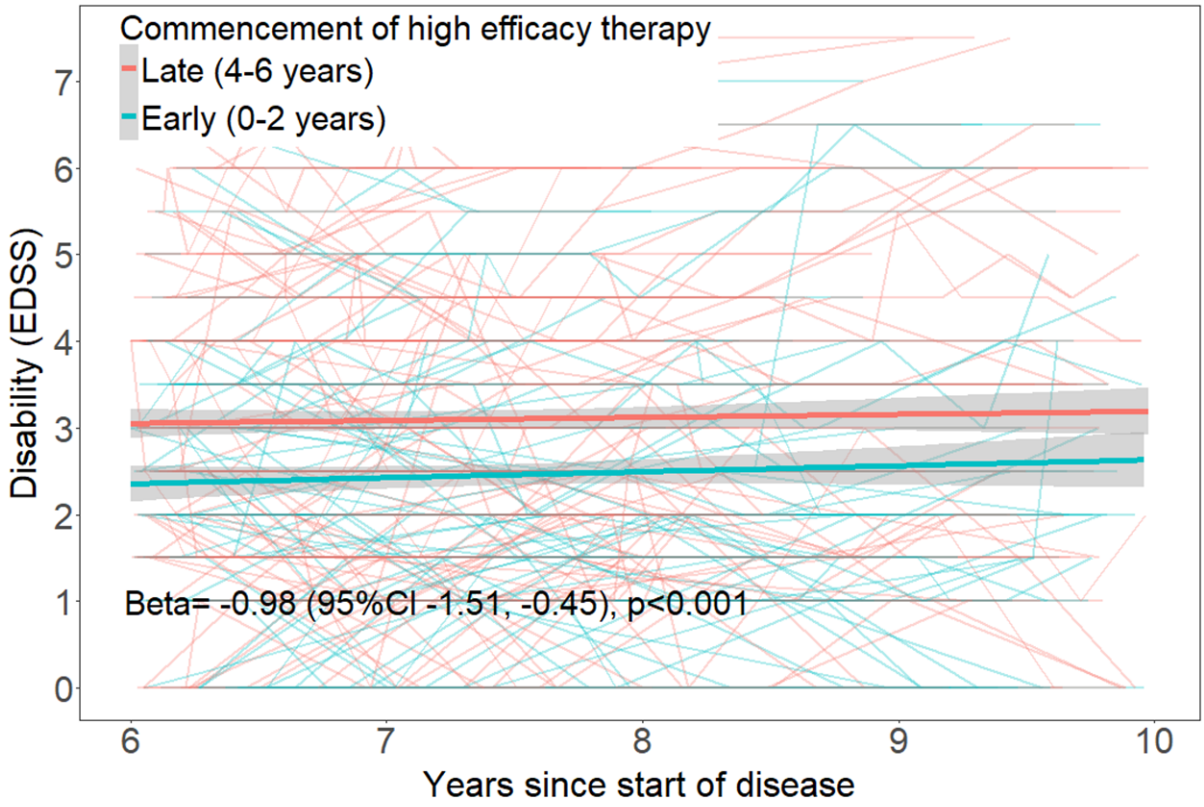
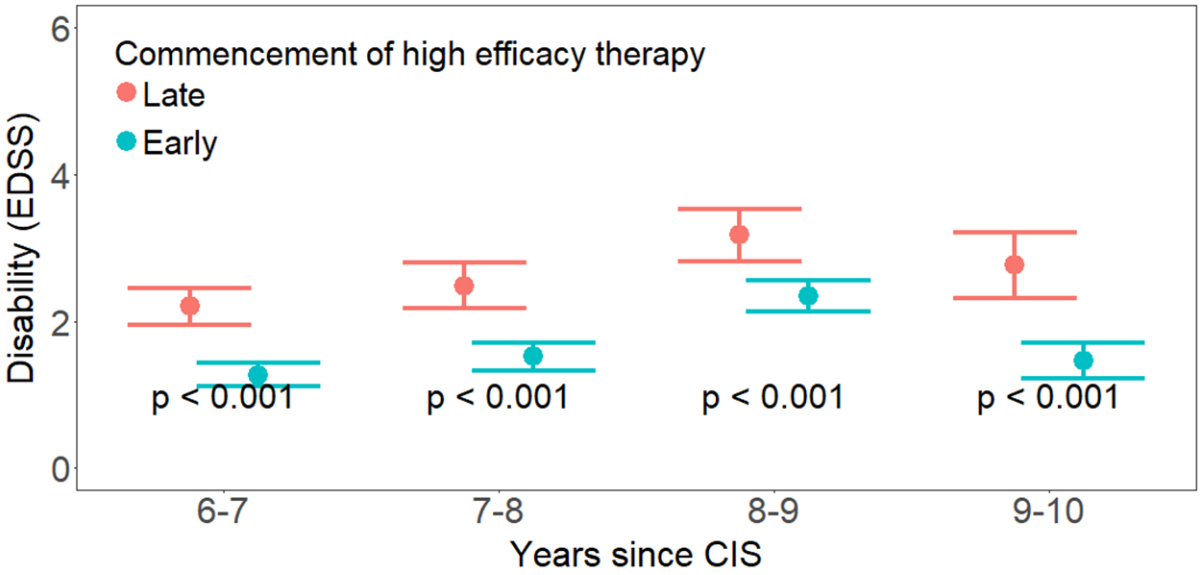


Figure 2B: Annual disability scores 6-10 years after onset of relapsing-remitting multiple sclerosis treated early versus late with ROMAN.



Number of patients				
Late	233	192	168	135
Early	189	140	126	89
% patients above EDSS 6				
Late	6.00	8.20	9.90	11.00
Early	2.60	2.10	3.20	3.40

Figure 3A: Cumulative hazard of disability progression from commencement of first disease-modifying therapy in patients treated early versus late with ROMAN therapy

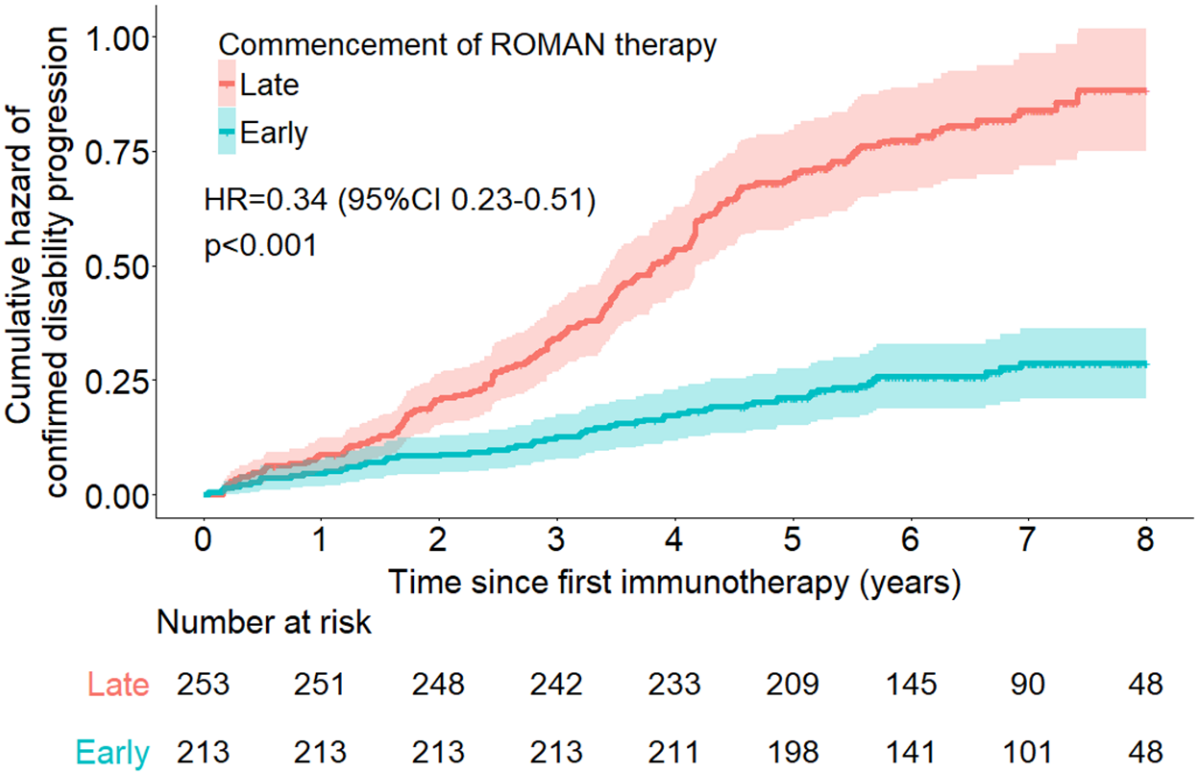


Figure 3B: Cumulative hazard of disability progression from disease onset in patients treated early versus late with ROMAN therapy

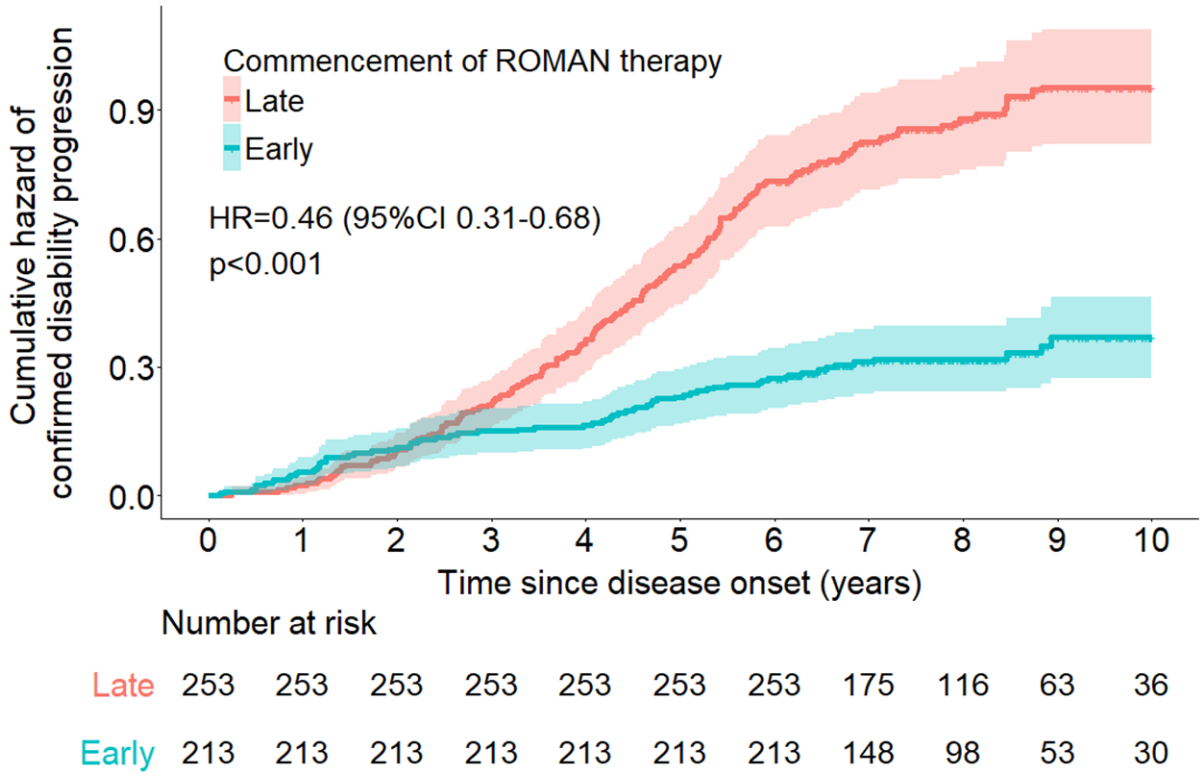


Figure 3C: Cumulative hazard of disability progression from the sixth year after disease onset in patients treated early versus late with ROMAN therapies

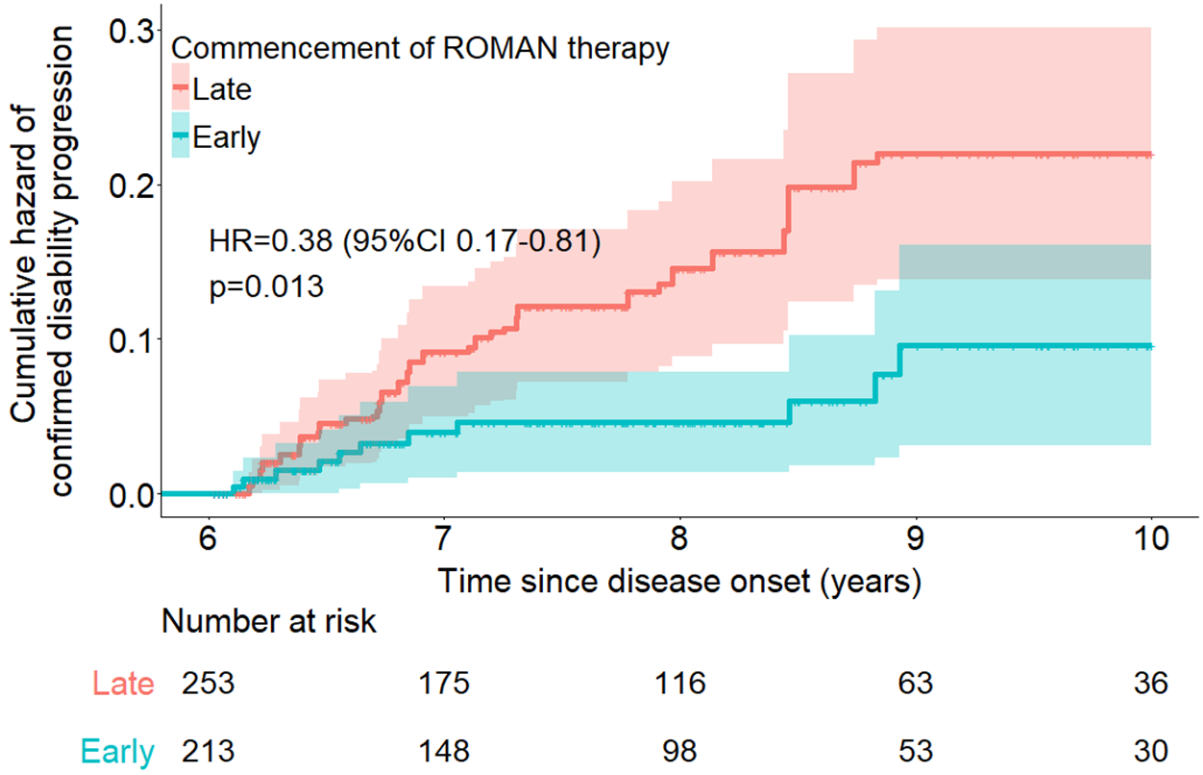


Figure 3D: Treatment persistence on ROMAN therapies in patients treated early versus late