1 ABSTRACT

Title

A Non-Interventional Post-Authorisation Safety Study to Investigate the Risk of Mortality in Multiple Sclerosis Patients Treated With Alemtuzumab (LEMTRADA®) Relative to Comparable Multiple Sclerosis Patients Using Other Disease Modifying Therapies: A Cohort Study.

Keywords

Post-Authorisation Safety Study, alemtuzumab, LEMTRADA, relapsing remitting multiple sclerosis (RRMS), highly efficacious disease modifying therapies (HE-DMTs), mortality.

Rationale and Background

In 2019, LEMTRADA was subject to a European Commission (EC) triggered procedure under Article 20 of Regulation (EC) No 726/2004 in which new and cumulative safety data were assessed by the European Medicines Agency pharmacovigilance risk assessment committee. The procedure concluded that LEMTRADA was associated with new and emerging safety events; cardiovascular adverse events (temporally associated with infusion) and additional autoimmune events. Additional data were required to assess the risk of mortality.

This final analysis report compares the risk of mortality in LEMTRADA treated multiple sclerosis (MS) patients with the risk of mortality in comparable MS patients, i.e., those treated with other HE-DMTs, based on secondary use of data from 2013 to 2023.

Research Question and Objectives

Research question: What is the risk of mortality in MS patients treated with LEMTRADA as compared to MS patients treated with other HE-DMTs?

Primary Objective: To ascertain whether MS patients treated with LEMTRADA had a higher risk of all-cause mortality than comparable MS patients treated with other HE-DMTs.

Secondary Objective: To examine the cause of death in data sources where this information was available and when the number of cases for a specific cause was sufficient for formal examination. This objective was exploratory as availability and quality of cause-specific mortality data was variable across data sources.

Study Design

This was an observational comparative cohort study based on the secondary use of data.

Setting

Routine care settings in Denmark, Sweden, Czech Republic, United Kingdom (UK), and Germany.

Subjects and Study Size

Eligible patients were MS patients who initiated LEMTRADA or other HE-DMTs after the date of LEMTRADA approval/reimbursement in each country.

All eligible patients were included to obtain the largest sample size possible.

Variables and Data Sources

Data sources

The data sources for this study consisted of MS patient registries, prescription/administrative data, and clinical chart data in European countries that each respectively hold data on patient characteristics, MS clinical parameters, therapies, vital status, as well as data on potential confounders such as cardiovascular comorbidities.

Variables

Cohort entry date (CED): the date of initiation of an HE-DMT after the date of LEMTRADA approval/reimbursement in the country.

Follow-up (FU) time: start of FU was at CED; end of FU corresponded to the earliest of: date of last update of vital status in each data source, death, emigration, or the end of data collection. For the As-Treated (AT) analysis (main analysis), FU additionally ended at switch date.

Exposure: MS patients initiating LEMTRADA were the exposed group (LEMTRADA cohort) and MS patients initiating HE-DMTs other than LEMTRADA were the compared group (HE-DMT_NL cohort).

Outcome: All-cause mortality (for primary objective) was a binary variable (death) measured by the recorded date of death. The cause of death (for secondary objective) was described where this information was available.

Covariates: Core variables e.g., demographics, MS clinical characteristics and comorbidities, all measured at CED were used to adjust (using propensity score [PS] weighting method) the association between exposure and mortality risk in the main analysis. In data sources where core variables were not recorded, proxy variables were used, e.g., the Expanded Disability Status Scale (EDSS) was not available in Germany and was replaced by a disability proxy variable.

Statistical Methods

Patients' characteristics and risk factors were summarised by exposure group (LEMTRADA cohort versus HE-DMT_NL cohort) at CED, to describe the study population and to evaluate the comparability of the study cohorts.

Propensity score methods

To address confounding, a PS was developed and used in weighted analyses. The PS model was constructed based on core variables measured at CED.

After exclusion of patients in non-overlapping regions of the PS, and after standardised mortality ratio (SMR) PS weighting had been applied, the balance for variables between the two cohorts was evaluated using standardised mean differences (SMDs). Comparing the effective sample size (ESS) to the original HE-DMT_NL cohort size was also used to evaluate the degree of comparability of the cohorts. The target of inference of study results was the average treatment effect among patients treated with LEMTRADA (average treatment effect among treated [ATT] approach).

Computation of mortality rates

In each data source, crude mortality rates (CMRs) were calculated for each exposure group (LEMTRADA and HE-DMT_NL) at the end of the AT FU time. CMRs were computed for all MS patients and by gender. Mortality rates were expressed as number of deaths per 100,000 person-years (PY) with 95% confidence intervals (CIs). A rate difference was also calculated for CMRs.

Computation of mortality risks

Risk of death among the LEMTRADA cohort compared to the HE-DMT_NL cohort was expressed as a hazard ratio (HR) from a Cox proportional hazard (PH) model that included exposure and PS weights at CED. Corresponding 95% CIs were computed. In case of remaining imbalance for some variables, a doubly robust method was applied to address residual confounding.

Sensitivity analyses

Sensitivity analyses for the final analysis included an Intent-to-Treat (ITT) analysis, restriction to RRMS patients, restriction to HE-DMT naïve patients, exclusion of patients with missing data on core variables (Sweden and UK only), and restriction of the HE-DMT_NL cohort to infused therapies and subcutaneous therapies and cladribine. The intention of the restricted models was to address confounding by indication using design methods rather than statistical adjustment. It was intended that multiple sensitivity analyses may help to understand confounding structures in the main model.

Results

Patients

The number of LEMTRADA initiators per country ranged from 56 to 457 patients, totalling 1183 LEMTRADA-treated patients across all the studied countries (Denmark: 134 patients,

Germany: 410 patients, Czech Republic: 126 patients, Sweden: 56 patients, UK: 457 patients). In total, 27,573 HE-DMT_NL-treated patients were included, where the largest number was in Sweden (Denmark: 5770 patients, Germany: 9532 patients, Czech Republic: 503 patients, Sweden: 10,511 patients, UK: 1257 patients). The total mean FU time in the AT approach was 5.7 years for the LEMTRADA-treated patients (range of means across data sources: 4.9 – 6.3 years), and 4.7 years for the HE-DMT_NL patients (range of means across data sources: 3.8 – 5.7 years).

With respect to LEMTRADA usage (LEMTRADA cohort), most patients in Denmark (98.5%), Germany (97.6%) and Sweden (100%) had initiated LEMTRADA prior to April 2019; 36.5% of patients in the Czech Republic and 11.2% of patients in the UK initiated treatment after April 2019. Patients treated with LEMTRADA were predominantly female in all countries (ranged between 64.30 – 76.59% across countries) and were on average in the mid-thirties (range of mean age: 33.50 – 36.2 years), except for Denmark where the mean (SD) age was 39.3 (8.7) years.

Patient Characteristics in the LEMTRADA Cohort – Variation Between Countries

There were differences at cohort entry, by country, with respect to patient phenotype in the LEMTRADA cohort. On one hand, in the UK, most LEMTRADA-treated patients (93.7%) were naïve to other HE-DMTs, had low levels of disability (EDSS < 2.25 for 52.5% of the LEMTRADA cohort), and the mean (SD) MS disease duration was 5.3 (5.3) years. In contrast, for Denmark, few LEMTRADA-treated patients (19.4%) were naïve to other HE-DMTs, a minority had low levels of disability (EDSS < 2.25 for 20.1% of the LEMTRADA cohort), and the mean (SD) MS disease duration was 12.2 (6.8) years. In Germany, the Czech Republic, and Sweden, half of the LEMTRADA-treated patients were naïve to other HE-DMTs (mean range of 48.2 – 49.8%), and no consistent pattern was observed for EDSS or duration of MS at the time of LEMTRADA initiation.

Comparison of Patient Characteristics between the HE-DMT_NL and LEMTRADA Cohorts

Comparing the LEMTRADA and HE-DMT_NL cohorts, differing patterns emerged between the countries. In Denmark, Germany, the Czech Republic, and Sweden, the patients treated with LEMTRADA were less frequently naïve to other HE-DMTs than the patients in the HE-DMT_NL cohort (Denmark: 19.4% versus 85.5%, Germany: 49.76% versus 85.73%, Czech Republic: 48.4% versus 58.3%, Sweden: 48.2% versus 83.9%, respectively). In Denmark, the LEMTRADA-treated patients had longer MS duration at CED than patients in the HE-DMT_NL cohort (mean [SD]: 12.2 [6.8] years versus 8.9 [8.2] years, respectively) and fewer LEMTRADA-treated patients had lower disability levels than patients in the HE_DMT_NL cohort (EDSS < 2.25: 20.1% versus 46.6%, respectively).

The opposite was observed in the UK where, in both the LEMTRADA and HE-DMT_NL cohorts, a similar proportion of patients were naïve to HE-DMTs (93.7% versus 95.2%, respectively). LEMTRADA-treated patients had shorter MS duration at CED than patients in

the HE-DMT_NL cohort (mean [SD]: 5.3 [5.3] years versus 8.0 [7.4] years, respectively) and lower levels of disability (EDSS < 2.25: 52.5% versus 33.6%, respectively).

In all countries, patients treated with LEMTRADA were 1 –7 years younger than patients in the HE-DMT_NL cohort.

Propensity Score Modelling

After PS weighting, the ESS for the HE-DMT_NL cohort was smaller than the original cohort size in each country (Denmark: 4351 patients versus 564.6 patients, Germany: 9464 patients versus 2313.2 patients, Czech Republic: 450 patients versus 230.3 patients, Sweden: 6683 patients versus 1825.0 patients, UK: 1011 patients versus 211.4 patients). The combined ESS for the HE-DMT_NL cohorts for the five countries (n = 5144.6) represented 23% of the original 27,573 patients before PS weighting.

After PS weighting, the LEMTRADA and HE-DMT_NL cohorts were balanced on core variables (SMD < 0.1) in all countries except for the UK, where the PS-weighted HE-DMT_NL cohort (compared to the LEMTRADA cohort) showed patients were less frequently naïve to HE-DMTs (89.5% versus 93.5%, respectively) and fewer patients had lower level of disability (EDSS < 2.25: 48.0% versus 53.8%, respectively). In all countries, multiple non-core variables remained imbalanced (SMD ≥ 0.1) after PS weighting, including variables on the number of prior HE-DMTs, relapses and hospitalisations, typically in the direction of more morbidity in the LEMTRADA cohort.

Mortality Rates

Few deaths were observed in the LEMTRADA cohort: < 5 deaths in Denmark, 7 deaths in Germany, 1 death in the Czech Republic, 2 deaths in Sweden and 3 deaths in the UK. In the HE-DMT_NL cohort, 59 deaths were observed in Denmark, 119 deaths in Germany, no deaths in the Czech Republic, 153 deaths in Sweden and 11 deaths in the UK.

For the LEMTRADA cohort, the CMR per 100,000 PY was 340.77 (95% CI: 88.32, 593.21) in Germany, 161.42 (95% CI: 0, 477.8) in the Czech Republic, 527.20 (95% CI: 0, 1257.9) in Sweden, and 104.59 (95% CI: 0, 222.9) in the UK. The CMR for the LEMTRADA cohort in Denmark was not revealed due to a requirement for masking small cells (<5) in the Danish data. The CMR per 100,000 PY in the HE-DMT_NL cohort was 221.48 (95% CI: 165.0, 278.0) in Denmark, 331.91 (95% CI: 272.27, 391.54) in Germany, 257.25 (95% CI: 216.5, 298.0) in Sweden and 206.06 (95% CI: 84.3, 327.8) in the UK. The CMR in the Czech Republic was not evaluable since there were no deaths in the HE-DMT_NL cohort.

Mortality Risks

The primary comparative mortality analyses (doubly robust PS-weighted Cox PH model using an AT censoring approach) were estimable for Denmark, Germany, Sweden and the UK.

The HRs comparing LEMTRADA to the HE-DMT_NL cohort in the main analysis was 0.85 (95% CI: 0.22, 3.23) in Denmark, 2.20 (95% CI: 1.00, 4.81) in Germany, 4.07 (95% CI: 1.00, 16.58) in Sweden and 0.63 (95% CI: 0.15, 2.72) in the UK. For the Czech Republic, the HR was not evaluable as there were no deaths in the HE-DMT_NL cohort.

For all countries (expect the Czech Republic, where HR was not evaluable), some of the Cox PH model assumptions were violated, as informed by the Schoenfeld residuals plot and/or crossing Kaplan-Meier (KM) curves testing the PH assumption, the deviance residuals plot

detecting the presence of influential outliers, and the martingale residuals plot (if applicable) testing the linearity assumption. Additionally, the low event rates added to concerns regarding the instability and non-interpretability of the HR estimates.

The results from the sensitivity analyses were similar to the results of the main analyses: the point estimates for the HRs were of similar magnitude and overlapped with the 95% CIs of the main analyses. However, the sensitivity analyses were hampered by the same Cox PH model violations as the main analyses.

A meta-analysis was considered inappropriate because key requirements were not met.

Cause of Death

In the Czech Republic there was one death in the LEMTRADA cohort caused by sepsis, 2 years and 6 months after LEMTRADA initiation. In Sweden, there were two deaths in the LEMTRADA cohort; one death caused by MS (further investigation revealed the cause was cytomegalovirus [CMV]) which occurred 11 days after LEMTRADA initiation; the other death was due to suicide 2 years and 8 months after LEMTRADA initiation. In the UK, there were three deaths in the LEMTRADA cohort; one death caused by acute myocardial infarction 4 years and 8 months after LEMTRADA initiation, one death caused by aspiration pneumonia 18 months after LEMTRADA initiation (related to glioblastoma multiforme diagnosis received prior to initiating LEMTRADA), and one death was reported with unknown cause (further investigation confirmed aspiration pneumonia) 5 years and 6 months after LEMTRADA initiation. The causes of death in the HE-DMT_NL cohorts in Sweden and the UK included suicide, cancer, accident and MS. There were no deaths in the HE-DMT_NL cohort in the Czech Republic. The causes of death were not available for Denmark or Germany.

Discussion

In four out of the five included countries (Germany, Denmark, Sweden, and the Czech Republic), LEMTRADA was increasingly used as non-preferred or last-line therapy throughout the study period. In the fifth country (UK), LEMTRADA was used early in the disease, per clinical trial evidence. Differing patterns of CMR were observed across the five countries, dependent on whether LEMTRADA was used early in MS disease or not. The CMR was lowest in the UK where LEMTRADA was used early in MS, and higher in the remaining countries where LEMTRADA was used as a non-preferred or last-line treatment. In the UK, the mortality rate for the LEMTRADA-exposed patients was approximately half of that observed in the HE-DMT_NL cohort, although the 95% CIs overlapped. Within every country, the 95% CIs overlapped between the LEMTRADA and HE-DMT_NL cohorts. The CMRs for the patients in the LEMTRADA cohort of this Post-Authorisation Safety Study (PASS) were consistent with the CMRs for LEMTRADA-treated patients from other ongoing and completed studies for LEMTRADA, as well as CMRs for other similar MS populations reported in the literature.

The results from the planned formal statistical modelling on the risk of mortality could not be interpreted due to: 1) the low event rate, 2) violation of model assumptions, and 3) persistent intractable confounding by severity of disease.

The low event rate (17 or fewer deaths in total for LEMTRADA) negatively impacted the stability of country-specific Cox PH models, although it is important to note that ultimately, a

low number of deaths in a study assessing potential excess mortality was a positive finding. Concerns on confounding came from the differences between LEMTRADA and HE-DMT_NL cohorts at CED, reduced ESS, the inability of sensitivity analyses to assuage concerns on confounding in the main model and suspected unmeasured confounding which, by its nature, could not be addressed.

Conclusion

This report presents the final results of a multi-country PASS, which aimed to assess mortality associated with exposure to LEMTRADA. These data represent 1183 LEMTRADA-patients with average FU for 5.7 years and 27,464 HE-DMT_NL patients with average FU for 4.7 years.

Although formal statistical models could not be interpreted, the descriptive data from this PASS offered valuable insight into mechanisms underpinning mortality as a serious adverse event in LEMTRADA-exposed patients.

In four out of the five included countries (Germany, Denmark, Sweden, and Czech Republic), LEMTRADA was used as non-preferred therapy. This pattern of use provided insight into the MS phenotypes exposed to LEMTRADA and the underlying risk of poor outcomes in that highly selected population. Conversely, in the UK, where the drug was still used in line with clinical trial evidence, the mortality rate for LEMTRADA-exposed patients was approximately half that observed in the relative HE-DMT_NL cohort, although the 95% CIs between the two cohorts overlapped. The mortality rate observed for LEMTRADA patients in the UK was also lower than the other included countries in this report, albeit with overlapping CIs. While this was based on low event rates with wide 95% CIs that overlapped with those observed in the HE-DMT_NL cohort, these results likely reflected the use of LEMTRADA as a non-preferred HE-DMT in Germany, Denmark, Sweden, and Czech Republic.

In conclusion, these final results provide insight into the heterogeneous patterns of prescribing for LEMTRADA, the underlying exposed population in each country, and how this impacted the observed mortality rates. In countries where the drug was used as a last-line or non-preferred agent, higher mortality rates were observed than when the treatment was used in line with clinical trial evidence, i.e., earlier in MS. In conclusion, these final results did not provide evidence for an increased risk of mortality in the LEMTRADA cohort versus the HE-DMT_NL cohort.

Marketing Authorisation Holder

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