P816

Real-world effectiveness of alemtuzumab in RRMS patients in Germany: Interim results of the TREAT-MS study after completion of recruitment

Tjalf Ziemssen[1], Frank Hoffmann[2], Stephan Richter[3], Ulrich Engelmann [4], Laura M. Quint[4]; on behalf of the TREAT-MS Study Group

[1]Center for Clinical Neuroscience, University Hospital Carl Gustav Carus, Dresden, Germany; [2]Department of Neurology, Hospital Martha-Maria Halle-Doelau, Halle (Saale), Germany; [3]Center for Neurology and Psychiatry, MIND, Stuttgart, Germany; [4]Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany

OBJECTIVE

- **To report interim results of real-world effectiveness of alemtuzumab of the ongoing TREAT-MS study (non-interventional long-Term study foR obsErvAtion of Treatment with alemtuzumab in active relapsing-remitting MS).**

CONCLUSIONS

- **This interim analysis of the TREAT-MS study indicates that patients benefited rapidly from alemtuzumab treatment regardless of timing of treatment initiation. EDSS scores remained stable and relapse rates low within a mean observational time of 3.3 years.**
- **The data confirm registration trial findings (CARE MS I and II) in the real-world setting in patients with varying treatment histories and longer treatment duration prior to switching to alemtuzumab.**
- **No new safety signal was observed.**

INTRODUCTION

- Alemtuzumab is a CD52-directed cytoloytic monoclonal antibody allowing for depletion of CD52-expressing cells and subsequent repopulation, intended to improve the long-term outcomes of multiple sclerosis (MS) patients.
- In the phase III CARE-MS I and II trials (NCT00530348; NCT00548405), alemtuzumab demonstrated significantly greater improvements in clinical and magnetic resonance imaging (MRI) outcomes versus subcutaneous interferon beta-1a (SC IFNβ-1a) over 2 years.[1,2] Efficacy was maintained over a 4-year extension (CAMMS03409; NCT00930553).[3] Maintenance over a 7-year extension was demonstrated in the CARE-MS II follow-up (TOPAZ study)[4,5]
- Although >1,400 patients have been treated with alemtuzumab in clinical trials, real-world data are still limited.
- The TREAT-MS study contributes real-world data on alemtuzumab use under routine practice conditions in Germany. Compared with patients in the CARE-MS trials, TREAT-MS patients have a longer disease duration and are more likely to have received DMT prior to enrollment.[6]
- Adverse events (AEs) associated with alemtuzumab treatment in clinical trials and post-marketing experience include[1,2,7]
  - Infusion-associated reactions,
  - Increased frequency of infection and the potential for opportunistic infections,
  - Secondary autoimmunity (thyroid disorders, immune thrombocytopenia [ITP], nephropathies, autoimmune hepatitis, autoimmune cytopenias and other less common autoimmune conditions),
  - Acute acalculous cholecystitis,
  - Cardiovascular and pulmonary events possibly related to infusion.

METHODS

Study Design

- TREAT-MS (Paul-Ehrlich-Institute registry: 281) is a multicentre, open-label, non-interventional long-term study that collects data from adult patients in Germany with active RRMS who are receiving treatment with alemtuzumab according to the approved SmPC.[7,8]
- Data are collected retrospectively and prospectively. Patients are followed-up for up to 48 months after the last treatment course.
- Alemtuzumab is administered according to local labelling as 2 annual courses (on 5 consecutive days at baseline and on 3 consecutive days 12 months later) with up to 2 additional courses (on 3 consecutive days) as needed ≥ 12 months after the prior treatment course.[7]

Interim Analysis

- This 5th interim analysis was conducted after end of recruitment (December 2020). Interim results show the total patient population (data cut-off: 02 February 2021).

RESULTS

Patients

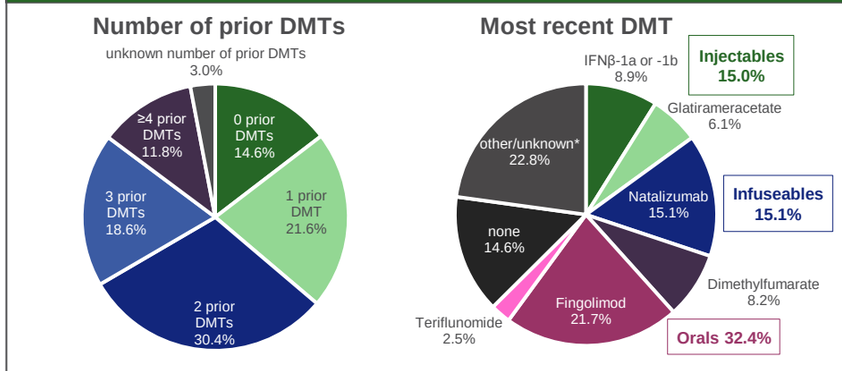
- In total, 907 patients were enrolled. As of February 2021, 899 (99.1%) entered the 1st and 771 (85.0%) the 2nd treatment period.
- Mean (SD) duration from 1st to 2nd treatment course was 1 (0.1) year. Mean (SD) observational time after the 2nd treatment course was 2.6 (1.3) years.
- Baseline characteristics and medical history are shown in **Table 1**.
- Most patients (82.4%) had received prior disease-modifying therapies (DMTs); about every seventh patient (14.6%) was treatment-naïve. Most frequently used DMTs immediately prior to enrolment were fingolimod (21.7%) and natalizumab (15.1%) (**Figure 1**).

Table 1. Baseline Characteristics and Medical History

Characteristic	Mean (SD)*
Age [years]	35.7 (9.2)
Age [years], median (range)	35.0 (16.0-63.0)
Female, n (%)	653 (72.0)
Male, n (%)	254 (28.0)
EDSS	2.8 (1.7)
EDSS, median (range)	2.5 (0.0-7.5)
Time since first MS symptoms until study inclusion [years]	8.1 (6.8)
Time since MS diagnosis until study inclusion [years]	7.3 (6.3)
Relapses during last 12 months before study inclusion	1.6 (1.2)

*Unless noted otherwise. Abbr.: EDSS, Expanded Disability Status Scale

Figure 1. MS Treatment History

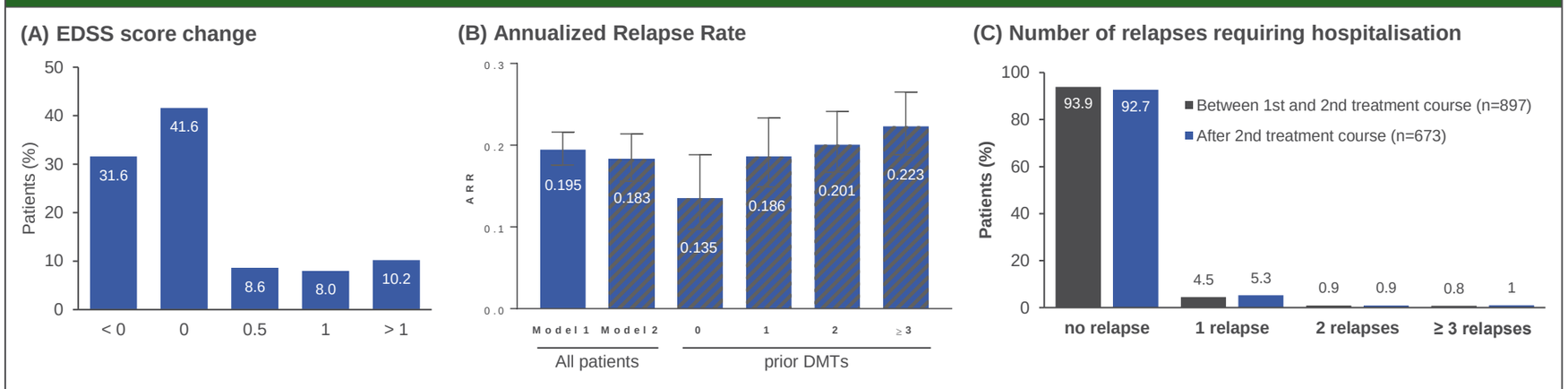


Percentages may not sum to 100% due to rounding; *includes rituximab (n=1), mitoxantrone (n=2), unknown (n=32), other (n=79), and not identifiable out of several pretreatments (n=93).

Effectiveness

- The first Expanded Disability Status Scale (EDSS) assessment was for most (96.7%) patients the 1st pretreatment visit. The mean (SD) duration from the first to the last assessment was 2.9 (1.6) years.
- The mean (SD) change from baseline in EDSS was -0.1 (1.4) points indicating slight disease improvement in patients evaluable (n=734).
- EDSS remained stable (change from baseline ≤ 0) in 73.2% of patients. EDSS progression (change from baseline > 0.5) was observed in 18.2% of patients (**Figure 2 A**).
- 6-month confirmed disability progression (CDP; ≥ 1.5-point EDSS score increase if baseline EDSS=0, ≥ 1-point increase if baseline EDSS=1-5, or ≥ 0.5-point increase if baseline EDSS>5) and improvement (CDI; defined similar by EDSS score decrease) was evaluated for 756 patients. 82.1% of patients were free of 6-month CDP, and 24.1% achieved 6-month CDI.
- Within a mean (SD) observational period of 3.3 (1.5) years, 67.2% of patients were relapse-free. For 32.8% of patients, at least one relapse was documented after start of alemtuzumab, resulting in an estimated annualized relapse rate (ARR) of 0.1950 (95% CI 0.1760; 0.2162). The ARR adjusted for the number of prior DMTs was similar (0.1827; 95% CI 0.1562; 0.2138). Even patients who had received ≥ 3 prior DMTs had a low ARR (0.2234; 95% CI 0.1882; 0.2652) (**Figure 2 B**). For 93.9% and 92.7% of the patients evaluable for the respective time periods, respectively, no relapses requiring hospitalisation were documented between the 1st and 2nd treatment course or after the 2nd treatment course with alemtuzumab (**Figure 2 C**).

Figure 2. Clinical Outcomes



(A) EDSS (Expanded Disability Status Scale) data were updated and slightly deviate from the respective data in the abstract; EDSS was missing in 173 patients. **(B)** Poisson regression model (transformed values); dependent variable: number of relapses; model 2 includes the independent variable "number of prior DMTs"; error bars indicate confidence interval (95% CI).

Safety

- As of 15 January 2021, AEs were reported for 66.8% of patients including 26.5% of patients with documented serious adverse events (SAEs) (**Table 2**).
- Infections were reported for 37.8% of patients with nasopharyngitis (11.8%) and urinary tract infection (11.1%) being the most frequent.
- Other frequent AEs included headache (15.1%) and rash (11.6%).
- Autoimmune AEs were mainly thyroid disorders and ITP
  - Endocrine disorders (mainly thyroid) were reported for 21.2% of patients with hyperthyroidism (6.3%), Basedow's disease (5.3%), hypothyroidism (5.3%) and autoimmune thyroiditis (5.2%) being the most frequent.
  - 16 cases (1.8%) of ITP (including 8 serious cases), 1 case (0.1%) of thrombotic thrombocytopenic purpura (TTP) and 2 cases (0.2%) of autoimmune haemolytic anaemia were reported.
  - 1 case (0.1%) of progressive multifocal leukoencephalopathy (PML) was reported who had relevant pretreatment (natalizumab-associated PML).
  - 1 case (0.1%) of autoimmune hepatitis was reported.
  - No cases of nephropathy were reported.
  - 2 cases (0.2%) each of serious cerebrovascular and cardiovascular events were reported.
- There were 3 deaths:
  - One occurred in a 33-year-old patient diagnosed with autoimmune hemolytic anemia and disseminated necrotizing leukoencephalopathy (DNL) 8 months after receiving treatment course 1, as reported previously.[9]
  - The second, of unknown cause, occurred in a 50-year-old patient who was found at home 1 month after receiving treatment course 1 (additional details not available).
  - The third occurred in a 33-year-old patient diagnosed with sepsis and multiple organ dys-function syndrome (3 years and 4 months after treatment course 2) and subdural haematoma (3 weeks later); previous SAEs included ITP (13 months after treatment course 2) and pulmonary embolism (14.5 months after treatment course 2; classified as not related).

Table 2. Adverse events

Patients with AE	n (%)
Any AE	606 (66.8)
AE related to alemtuzumab	525 (57.9)
AE of special interest*	173 (19.1)
Any SAE	240 (26.5)
SAE related to alemtuzumab	131 (14.4)
Death	3 (0.3)

*AEs of special interest were defined as pregnancy, symptomatic overdose, anaphylaxis, opportunistic infections including progressive multifocal leukoencephalopathy, disseminated infections, transaminase elevations, cytopenias, malignant diseases, cervical dysplasia, or autoimmune diseases including ITP and nephropathies.

References

1. Cohen JA, et al. Lancet 2012; 380:1819-28.; **2.** Coles AJ, et al. Lancet 2012; 380:1829-39.; **3.** Coles AJ, et al. Ther Adv Neurol Disord 2021; 14:1-7.; **4.** Montalban X et al., Mult Scler 2019; 25(S2):357-580, P974; **5.** Comi G et al., Mult Scler 2019; 25(S2):131–356, P645; **6.** Ziemmsen T, et al. Front Neurol 2021; 12:620758.; **7.** LEMTRADA [Summary of Product Characteristics] June 2021, Sanofi Belgium, Diegem, Begium.; **8.** Ziemmsen T, et al. BMC Neurology 2016; 16:109; **9.** Metz et al. Acta Neuropathol Commun 2016; 4:81

Acknowledgments and Disclosures

TREAT-MS Steering Committee. Editorial support for this poster was provided by Alcedis GmbH and was funded by Sanofi. TREAT-MS is sponsored by Sanofi. **TZ**: Research support, consulting fees and honoraria (Alexion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi, Teva); **FH**: Consulting and/or speaking fees (Alexion, Bayer, Biogen, CSL Behring, DIAMED Medizintechnik, Grifols, Ipsen, Merck, Novartis, Roche, Sanofi, Teva) and grant/research support (Bayer, Biogen, Merck, Novartis); **SR**: Travel grants and honoraria for lectures (Biogen, Celgene, Merck, Novartis, Roche, Sanofi Genzyme); **UE, LMQ**: Employees of Sanofi, who may hold shares and/or stock options in the company.

CARE-MS=Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis. Rebif® is a registered trademark of Merck Serono Europe Ltd.

Alemtuzumab is approved in >70 countries around the world for the treatment of relapsing forms of MS. In the EU, alemtuzumab is indicated as a single disease-modifying therapy (DMT) in adults with highly active RRMS; for patients with highly active disease despite a full and adequate course of treatment with at least 1 DMT or patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI. In the US, the indication provides that, because of its safety profile, the use of alemtuzumab should be reserved for patients who generally have had an inadequate response to 2 or more therapies indicated for the treatment of MS. This material may contain information that is outside of the approved labeling in some countries.

Presented at the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Digital Meeting, October 13-15, 2021

Funding provided by Sanofi