ALEMTUZUMAB

Tjalf Ziemssen
Center of Clinical Neuroscience, University Clinic Carl Gustav Carus, Dresden University of Technology, Dresden, Germany

Alemtuzumab is a humanized, monoclonal antibody that selectively targets CD52 to deplete circulating T and B lymphocytes, thought to be critical mediators of MS inflammatory processes. Following lymphocyte depletion, a distinctive pattern of T- and B-cell repopulation begins within weeks, changing the balance of the immune system. Innate immune cells are minimally or transiently impacted by alemtuzumab treatment. Although alemtuzumab's exact mechanism of action in MS is not fully elucidated, these pharmacodynamic changes may help explain its clinical effects in MS. In clinical studies, alemtuzumab was administered 12 mg/day via intravenous (IV) infusions on 5 consecutive days at baseline and on 3 consecutive days 12 months later. The novel annual dosing schedule of alemtuzumab results from its unique PK/PD profile and durability of effects on the immune system: serum alemtuzumab concentrations decreased to low or undetectable levels within 1 month after dosing in RRMS patients in clinical studies, while the effects persisted after alemtuzumab was cleared from the circulation.

The alemtuzumab clinical development program in relapsing-remitting multiple sclerosis (RRMS) consisted of one Phase 2 (CAMMS223, NCT00050778) and 2 Phase 3 studies: Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis (CARE-MS) I (NCT00530348) and II (NCT00548405). All studies compared alemtuzumab with subcutaneous interferon beta-1a (SC IFNB-1a) in RRMS patients with active disease (≥2 relapses in the prior 2 years and ≥1 relapse in the prior year). The co-primary endpoints were annualized relapse rate (ARR) and time to 6-month sustained accumulation of disability (6-month SAD, defined as an increase from baseline in EDSS score of ≥1.0 [≥1.5 in patients with a baseline EDSS score of 0], confirmed twice during a 6-month period). Patients completing the core studies were eligible to enroll in the CARE-MS extension study (NCT00930553), which is currently ongoing.

In the CARE-MS I study, which enrolled treatment naïve patients, alemtuzumab significantly reduced ARR by 55% vs. SC IFNB-1a ($p<0.0001$, ARR 0.18 vs. 0.39). Alemtuzumab reduced the risk of 6-month sustained accumulation of disability by 30% vs. SC IFNB-1a (alemtuzumab, 8.0% vs. SC IFNB-1a, 11.1%); however, this difference was not statistically significant. The inability to detect a treatment difference may be at least partially attributed to the lower-than-expected rate of SAD among SC IFNB-1a patients, since CARE-MS I was powered based on an expected 6-month SAD of 20% at 2 years for SC IFNB-1a based on data in the CAMMS223 trial.

In CARE-MS II, which enrolled patients who relapsed on prior therapy, alemtuzumab significantly reduced ARR (49% reduction vs. SC IFNB-1a [0.26 vs. 0.52; $p<0.0001$]) and risk of 6-month SAD (42% reduction vs. SC IFNB-1a [12.7% vs. 21.1%; $p=0.0084$]). Additionally, alemtuzumab significantly improved pre-existing disability vs. SC IFNB-1a (hazard ratio vs. SC IFNB-1a, 2.57; $p=0.0002$), as assessed by 6-month sustained reduction in disability (6-month SRD, defined as decrease from baseline by ≥1 EDSS point confirmed over 6 months for patients with baseline EDSS scores ≥2.0).

In addition to clinical benefits in RRMS patients with active disease, alemtuzumab has demonstrated benefits vs. SC IFNB-1a on MRI outcomes, including reduction in rate of brain atrophy, in both treatment-naïve patients and patients who relapsed on prior therapy.

Durability of effect with alemtuzumab has been demonstrated in data to date from the CARE-MS extension. As of November 26, 2012, all alemtuzumab-treated patients had been followed up for at least 3 years in the extension, representing 5400.7 patient–years of exposure. Although re-treatment with alemtuzumab was permitted during the extension, the majority of the former alemtuzumab-treated patients did not receive re-treatment during Year 3 (CARE-MS I, 82%; CARE-MS II, 80%), and <2% received other DMTs. Despite this, relapse rate remained consistently low in patients from both CARE-MS studies (0.24 in patients from CARE-MS I and 0.25 in patients from CARE-MS II) through Year 3 of the extension; furthermore, approximately 70% of alemtuzumab-treated patients had improved or stable disability scores at Year 3 vs. baseline. In patients originally enrolled in the CARE-MS II study who relapsed on prior therapy, the proportion of patients with sustained improvement in pre-existing disability continued to increase through Year 3 in the extension.

Alemtuzumab has a well characterized safety profile, which was consistent across the MS clinical development program (core studies and extension). Identified risks with alemtuzumab include infusion associated reactions (IARs), infections, and autoimmune adverse events (including thyroid events and,

less frequently, immune thrombocytopenia [ITP] and nephropathies). IARs (defined as any AE beginning during, or within 24 hours after, alemtuzumab infusion) were the most frequently reported AEs in clinical trials, occurring in >90% of patients; these were predominantly mild to moderate, reduced with steroid pre-treatment, and decreased with each alemtuzumab treatment course. While infections were more common following treatment with alemtuzumab than with SC IFNB-1a (CARE-MS I, 67% vs. 45%; CARE-MS II, 77% vs. 66%), most were mild-to-moderate and responded to conventional therapy; the incidence of serious infections was low (2.8% vs. 1.3% with SC IFNB-1a across CARE-MS I and II), consistent with the mechanism of action of alemtuzumab. Autoimmune AEs were identified early and successfully managed with standard treatment after the implementation of a safety monitoring program into the MS clinical development program, which included laboratory monitoring and patient and physician education.

The efficacy and safety results from the clinical development program in MS suggest that alemtuzumab has a favorable benefit:risk profile in appropriate patients; ie, RRMS patients with active disease.