THE EVOLVING MS LANDSCAPE: CHALLENGES AND OPPORTUNITIES

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Unmet Medical Needs in Multiple Sclerosis: Patient and Healthcare Perspectives

Professor Mefkûre Eraksoy

Historically, multiple sclerosis (MS) treatment goals have focused on clinical endpoints, delaying disability, and reducing relapse frequency, and magnetic resonance imaging (MRI) goals have focused on reducing and preventing new lesions.[1,2] Current treatments are preventive rather than restorative,[3] have limited impact on the accumulation of disability, and are only partially effective in preventing relapse.[4]

New treatments offer the opportunity to delay disability progression and relapses, but to address unmet needs one must consider the perspective of both the patient and the healthcare provider.[5-8] Patients require more tolerable therapies[9] that are easier to take,[10] and reduce the frequency of intravenous interventions.[10] They require customised treatments based on disease prognosis and individual needs[9,10-14] that provide quality of life (QoL) benefits.[12] Patients also require greater knowledge of the overall benefit/risk balance of the available treatments.[13] Health status deteriorates with increasing disability in a non-linear manner.[15-17] The initial steep progression as the patient moves from 0.5 to 2.5 on the expanded disability status scale (EDSS) slows between EDSS 2.5 and 6.0 before a rapid decline leading to EDSS 9.0. Early intervention is therefore important to limit disability and preserve health status.

Treatment can be better individualised by understanding what impacts a patient's QoL.[16] QoL is not based on function alone; it involves social, mental, and emotional aspects.[14,16,18-20] Treatment adherence is a major challenge. A survey of 2,648 patients revealed that adherence to injectable disease-modifying treatments (DMTs) declined the longer the patients received therapy.[9] Lack of adherence is largely due to injection-related issues, principally injection site pain, injection anxiety, and patients becoming tired of taking injections.[9] Furthermore, many patients simply forget to administer their drugs.[9]

Adherence plays a crucial role in long-term outcomes; adherent patients have a 60–70% risk reduction in relation to reaching EDSS 6; EDSS 6 combined with secondary progressive MS (SPMS), SPMS alone, or being confined to a wheelchair.[21]

Better involvement of patients in treatment decisions can improve adherence; however, physicians and patients place different emphasis on the importance of clinical attributes.[22] Physicians are primarily concerned with long-term outcomes, whereas patients are more concerned with the immediate impact of daily treatments on their disease and their QoL.[22] Importantly, patients may be more willing than their physicians to take risks in exchange for efficacy benefits.[13]

The course of MS is driven by inflammatory events, occurring early on, which predict long-term disability progression and highlight the need for early intervention rather than a 'wait and see' approach to optimise long-term outcomes.[23-29] Thus, early in the disease there is a therapeutic window when the greatest benefit can be obtained from the most appropriate intervention.[30] Individualising therapy relies on understanding the optimal patient prognosis to select the most appropriate treatment. Factors associated with good prognosis are younger age of onset, white ethnicity, female gender, isolated sensory systems, long interval to the second relapse, and low MRI lesion load at onset. Conversely, older age of onset, male gender, non-white ethnicity, involvement of efferent systems, large MRI lesion load at onset, and a rapid rate of accumulation of MRI lesions during the first 5 years are predictors of poor prognosis.[31] Not only is there considerable variation in the course of the disease but the response to treatment is heterogeneous. Up to 50% of patients have a suboptimal response to injectable therapies,[26] highlighting the need for markers of efficacy and safety to enable better individualised treatment. Switching treatment based on clinical and MRI disease activity is feasible and clinicians should strive for a disease activity-free response in patients with relapsing-remitting multiple sclerosis (RRMS).

Currently, there are no standardised guidelines or algorithms for choosing between the increasing number of DMTs available (11 as of 2014[32]). For many patients, the first treatment choice will not be the last; treatment is an ongoing decision requiring close monitoring. Consideration of the patients' needs, clinical presentation, prognosis, and the ultimate treatment goal offers a practical approach that can be implemented as individualised treatment. The traditional approach of starting all patients on the same moderate efficacy treatment options then cycling and escalating these as the disease progresses ignores the heterogeneities of the disease course or treatment response,[26,33,34] and is not appropriate for all patients.[26] Individualised treatment based on projected disease course is the basis of an evolving treatment paradigm;[33,35] one that considers the needs, disability and disease status, prognosis, and adherence potential of a patient from the outset,[35-37] and involves the patient in treatment decision-making. Individualised treatment relies on close and ongoing assessment to achieve freedom from disease activity.[36,37]

In summary, traditional treatment goals in MS have been strictly limited by the treatment available. New therapies can address the unmet needs of both physicians and patients, allowing a redefinition of treatment goals to include improving existing disability, reducing new MRI activity, and freedom from disease activity. Consideration of the patient's perspective allows individualised treatment, taking into account the willingness of patients to accept risks in exchange for greater efficacy, reduced treatment burden, and improved QoL.

New Oral Opportunities in First-Line MS Therapy: Teriflunomide

Professor Matthias Mäurer

Teriflunomide is the primary active metabolite of leflunomide, a drug used for the treatment of rheumatoid arthritis. Following an extensive clinical study programme,[8,38,39] a once-daily 14 mg dose of the novel formulation, teriflunomide, has been licensed for the treatment of RRMS in the European Union (EU)[22,40] and is under regulatory review in Turkey.[22] Teriflunomide inhibits a key enzyme of pyrimidine synthesis, thereby interrupting the pyrimidine supply of rapidly proliferating cells. Particularly, rapidly proliferating T and B cells are depleted of dihydro-orotate dehydrogenase (DHODH), a compound vital for RNA and DNA synthesis, cell membrane molecules, and second messengers.[41] In this regard, teriflunomide can be viewed as a selective immunomodulator rather than an immunosuppressive drug. Resting T cells and non-lymphoid cells are unaffected because they utilise the 'salvage pathway' to supply their pyrimidine pool.[41]

To date there have been ten clinical trials involving teriflunomide.[8,11,39,42-48] The TEMSO[8] and

the TOWER[42] studies examined teriflunomide at 7 mg and 14 mg versus placebo. The TENERE trial[43] examined teriflunomide versus the established MS treatment, Rebif. The TOPIC study[49] examined the efficacy of teriflunomide in clinically isolated syndrome. TERIPRO[46] is a multinational study evaluating the effect of teriflunomide on patient-related outcomes in clinical practice. The TERIKIDS trial[48] is evaluating the effect of teriflunomide in children and adolescents. TERIVA[44] and the Rabies neoantigen study[45] are examining vaccination with teriflunomide. These trials measure efficacy in three key areas: relapse rate, progression of disability accumulation, and MRI activity. Annualised relapse rate (ARR), the primary endpoint of TEMSO[8,38] and TOWER,[38,42] was significantly reduced by both the 7 mg and 14 mg doses of teriflunomide, with the latter reducing risk by 32-36%. Furthermore, unlike the 7 mg dose, the 14 mg dose significantly reduced disability accumulation in both trials.[8,38,42] Both doses produced significant reductions in gadolinium-enhancing (Gd) lesion loads of 57% and 80%, respectively.[8] In addition, the 14 mg dose significantly reduced total lesion volume by 67%.[8]

Data from the TEMSO and the TOWER populations were pooled to create a larger subgroup of patients with highly-active disease, defined as two or more relapses in the year before study entry. Both doses of teriflunomide significantly reduced severe relapses leading to hospitalisation, requiring IV corticosteroids, had sequelae, or were defined by Panlich's rules, with the greatest reductions associated with the 14 mg dose.[50] Such relapses have a significant impact on a patient's QoL as assessed by the SF-36 questionnaire.[49] Based on these data, the European Medicines Agency licensed teriflunomide for the treatment of MS for patients with RRMS without any restriction. Data from the TOPIC trial,[49] evaluating the effect of teriflunomide in patients with early MS or clinically isolated syndrome (CIS), show a 43% risk reduction for a further relapse in CIS. Despite failing to meet its primary endpoint - time-to-failure versus Rebif - the TENERE study[43] showed similar rates of relapse/treatment discontinuation for both drugs. Furthermore, there was no significant difference in ARR between subcutaneous interferon preparation and teriflunomide 14 mg.[43] Nevertheless, treatment satisfaction questionnaire for medication (TSQM) scores at week 48 demonstrated a clear advantage for teriflunomide in terms of side-effects and convenience, which may have important implications for adherence.[43]

Many patients do not want injectable therapies. Take for instance the case of a 28-year-old female who experienced a right optic neuritis, had complete remission after IV steroids and an EDSS of 0.0. Her MRI shows dissemination in time and space and she fits McDonald's 2010 criteria for definite MS. The patient needs a convenient and tolerable medication and wants children eventually. Therefore, teriflunomide meets all the criteria required for an individualised MS therapy. Pooled safety data show no difference between placebo and teriflunomide in the rates of serious infections and malignancies.[51] Side-effects include nausea, diarrhoea, hair thinning, and reduced neutrophil and lymphocyte counts that remain within the normal range.[8,42,51,52] Teriflunomide causes a slight elevation of liver enzymes and regular monitoring is mandatory.[51] Ongoing blood pressure and total blood count testing is also required, and women of child bearing age need to use contraception. Whilst there have been 26 live births with no malformations or structural or functional abnormalities of children exposed during gestation,[53] teriflunomide is contraindicated in pregnancy. Should a patient fall pregnant accidentally or wish to become pregnant, an accelerated elimination procedure using charcoal or cholestyramine can reduce teriflunomide concentrations by 98% in 11 days.[54] Two studies have addressed the effects of teriflunomide on vaccinations and demonstrated a normal seroprotective response to neoantigens (rabies)[44] and recall antigens (influenza).[39]

In summary, teriflunomide has a consistent efficacy in clinical and MRI outcomes across a broad spectrum of MS patients. Teriflunomide demonstrated significant benefits on disability in two separate placebo-controlled Phase III trials (TOWER and TEMSO). An extensive clinical programme with long-term follow-up provides a consistent and well characterised safety profile of teriflunomide. Taken together, the overall benefit/risk profile supports teriflunomide's use as an initial therapy for RRMS patients.

New Opportunities with Alemtuzumab: a Mechanism-Based Therapy for MS

Professor Alastair Compston

Alemtuzumab (Lemtrada) began life 23 years ago as Campath-1H. The original name reflects the fact that it was produced at the University of Cambridge and was the first humanised monoclonal

antibody. Based on the knowledge of the pathogenesis of MS in the late 1980s it was hypothesised that targeting the circulatory immune system might provide a viable treatment option. The hypothesis was first tested in a patient in 1991. Observations over the next decade led to the realisation that drugs targeting the immune system need to be given early in the course of the disease. Alemtuzumab performed well in the CAMMS223 Phase II study of patients with early MS designed in conjunction with Ilex, subsequently purchased by Genzyme. Data at 3 and 5 years were extremely positive and led to the Genzyme 2 Phase III studies, CARE-MS I and CARE-MS II. All trials have entered into extension phases and data are continuing to be gathered. Based on these trials, the EU granted a product licence on 17th September 2013 for the use of alemtuzumab in the treatment of adults with active RRMS as a first-line therapy. Alemtuzumab is also approved in Australia, Brazil, Canada, Guatemala, and Mexico.[22] An FDA licencing decision is due in December 2014 and reviews are taking place in several other countries; however, Turkey has not approved alemtuzumab.[22]

Alemtuzumab binds to CD52, a protein of unknown function, which is abundant on the surface of B and T lymphocytes.[55] Alemtuzumab is administered in two courses by IV infusion at 12 mg/day. The first course runs over 5 consecutive days and, 1 year later, the second course runs over 3 consecutive days.[56] Blood levels initially reach a high concentration that falls following the infusion. The drug is undetectable after 30 days following the first course and 14 days following the second.[57] Once the treatment is complete there is no withdrawal or requirement to reverse the drug. On the first 3 days of each course patients should be pretreated with conventional IV corticosteroids to avoid cytokine release syndrome leading to acute infusion reactions.[56] Patients should also be given acyclovir antiviral therapy for the first month of each treatment course.[56]

Alemtuzumab is a cytotoxic antibody that selectively targets the adaptive immune system by depleting T and B cells in the circulation,[55,58,59] sparing the neutrophils and monocytes of the innate immune system.[7] Following treatment, levels of CD4 T cells drop rapidly before recovering slowly; however, they remain below the lower limits of normal during the treatment period and for many years after that.[7] Depletion of the adaptive immune system creates an 'immunological space' that is repopulated to form an immune system with entirely different properties.[55,58-60] During repopulation there is a surge of regulatory T cells and the immunological space is filled by an expansion of surviving memory clones. This preferential memory cell expansion may bring back some old immunological memories that are probably responsible for alemtuzumab's main side-effect, secondary autoimmunity.

The initial treatment cohort treated between 1991 and 1997 consisted of 36 patients with relatively advanced secondary progressive MS who were already disabled. Following suboptimal results from these first patients, the next trial commenced in 1999 focusing on a cohort of 22 people with early RRMS.[61] Data from the secondary progressive MS and RRMS cohorts show that alemtuzumab reduced relapse rates by 98% and 91%, respectively.[61,62] Disability in the progressive MS cohort, as measured by EDSS, increased in the years following the course of alemtuzumab. Conversely, EDSS scores in the RRMS cohort actually fell in the majority of patients.[61] These results highlighted the need to treat patients early on in the course of the disease to achieve the best possible reduction in disability and this rationale was the basis of the subsequent multicentre international clinical trials.

The Phase II study, CAMMS223, and the Phase III studies, CARE-MS I and CARE-MS II, are randomised, comparator-controlled trials comparing alemtuzumab against a high dose of interferon beta-1a (Rebif) in patients with active RRMS. CAMMS223 and CARE-MS I focused on drug-naïve patients whereas patients in CARE-MS II had already relapsed on another therapy.[6,63,64] Over 94% of patients from CARE-MS I and II entered the extension study, and as of June 2014, patients have been followed for at least 4 years, representing over 6,500 patient-years of exposure.[6,63,64] CARE-MS I and II are well balanced in terms of disease duration, gender, number of attacks, and number of enhancing lesions. However, CARE-MS II includes higher levels of disability and longer disease durations.[64] CARE-MS I and II both reached their co-primary endpoint of ARR. Both trials achieved treatment effect over and above that achieved with Rebif, namely 55% for CARE-MS I and 49% for CARE-MS II.[6,64] Moreover, alemtuzumab proved superior in reducing the rate of severe relapse.[65,66]

The other co-primary endpoint concerned disability; alemtuzumab produced highly significantly lower rates of sustained accumulation of disability in CARE-MS II[64] and a pooled analysis of CARE-MS I

and CAMMS223.[67] Patients receiving alemtuzumab in CARE-MS II were more than twice as likely to have a sustained improvement in disability over 6 months.[6] Furthermore, mean EDSS scores at 2 years improved from baseline in patients receiving alemtuzumab and worsened in patients receiving Rebif.[64] Alemtuzumab also demonstrated significant reductions over Rebif in the proportion of patients with Gd-enhancing lesions, new or enlarged T2 and new T1 lesions.[68,69] However, reductions in T2 lesion volumes were not significant in CARE-MS I or II.[6,64] The proportion of patients free from disease activity, either measured using MRI or clinical parameters is - with the exception of MRI activity in CARE-MS I - significantly higher in both CARE-MS I and II.[6,70,71] Alemtuzumab-treated patients had significantly improved QoL at all time points.[72,73] Overall, approximately 80% of patients did not require a third alemtuzumab dose; <2% changed therapy.[65] Both ARRs remained low[6,7,65] and disability scores continued to improve after 3 years.[60] 12 year follow-up of the initial 87 patients shows 80% of the cumulative experience led to stability or improvement.[74]

The majority of adverse effects were mild-to-moderate and patients responded to conventional therapies; serious infections were rare.[22,64,75] The overall incidence of adverse effects and infections declined over 3 years.[76] The safety profile was similar in treatment-naïve patients and those who had received prior therapy. Acute infusion effects coincided with the two courses of treatment, and were fewer with the second course.[77,78] In addition to acute infusion reactions, alemtuzumab's main side-effect is secondary autoimmunity affecting the thyroid, with very rare cases of idiopathic thrombocytopaenic purpura and renal immunity.[79] As a result, there is a compulsory risk management plan to anticipate such complications.[56]

In summary, alemtuzumab demonstrates superior and durable efficacy (both clinical and MRI measures) and improvements of pre-existing disability. The drug has a consistent, well characterised safety profile with early detection and management of identified risk managed via a comprehensive safety monitoring programme. These data support a favourable benefit/risk profile for alemtuzumab in RRMS patients.

REFERENCES

1. IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology. 1993;43:655-61.

2. PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet. 1998;352:1498-504.

3. Linker RA et al. Identification and development of new therapeutics for multiple sclerosis. Trends Pharmacol Sci. 2008;29:558-65.

4. Goodin DS et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology. 2002;58:169-78.

5. Kappos L et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362:387-401.

6. Cohen JA 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.

7. Coles AJ et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380:1829-39.

8. O'Connor P et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365: 1293-303.

9. Devonshire V et al. The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. Eur J Neurol. 2011;18:69-77.

10. Patti F. Optimizing the benefit of multiple sclerosis therapy: the importance of treatment adherence. Patient Prefer Adherence. 2010;4:1-9.

11. Mäurer M et al. Impact of severe relapses on disability, fatigue and health-related quality of life outcomes: a pooled dataset of the phase 3 TEMSO and TOWER studies. ECTRIMS. 2013;P1093.

12. Lobentanz IS et al. Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. Acta Neurol Scand. 2004;110:6-13.

13. Johnson FR et al. Multiple sclerosis patients' benefit-risk preferences: serious adverse event risks versus treatment efficacy. J Neurol. 2009;256:554-62.

14. Lorefice L et al. What do multiple sclerosis patients and their caregivers perceive as unmet needs? BMC Neurol. 2013;13:177.

15. Orme M et al. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health. 2007;10:54-60.

16. Zwibel HL, Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. Am J Manag Care. 2011;17 Suppl 5 Improving:S139-45.

17. Naci H et al. The impact of increasing neurological disability of multiple sclerosis on health utilities: a systematic review of the literature. J Med Econ. 2010;13:78-89.

18. Rothwell PM et al. Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis. BMJ. 1997;314:1580-3.

19. Aronson KJ. Quality of life among persons with multiple sclerosis and their caregivers. Neurology. 1997;48:74-80.

20. Grossman P et al. MS quality of life, depression, and fatigue improve after mindfulness training: a randomized trial. Neurology. 2010;75:1141-9.

21. Goodin DS et al. Establishing long-

term efficacy in chronic disease: use of recursive partitioning and propensity score adjustment to estimate outcome in MS. PLoS One. 2011;6:e22444.

22. Genzyme. Data on file.

23. Compston A, Coles A. Multiple sclerosis. Lancet. 2008;372:1502-17.

24. Stüve O et al. Pharmacological treatment of early multiple sclerosis. Drugs. 2008;68:73-83.

25. Scalfari A et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain. 2010;133:1914-29.

26. Río J et al. Defining the response to interferon-beta in relapsing-remitting multiple sclerosis patients. Ann Neurol. 2006;59:344-52.

27. Brex PA et al. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med. 2002;346:158-64.

28. O'Riordan JI et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain. 1998;121(Pt 3):495-503.

29. Fisher E et al. Eight-year follow-up study of brain atrophy in patients with MS. Neurology. 2002;59:1412-20.

30. Miller JR. The importance of early diagnosis of multiple sclerosis. J Manag Care Pharm. 2004;10:S4-11.

31. Fernández O. Integrating the tools for an individualized prognosis in multiple sclerosis. J Neurol Sci. 2013;331:10-3.

32. European Medicines Agency. www.ema-europa.eu/ema/.

33. Miller A et al. Translation towards personalized medicine in multiple sclerosis. J Neurol Sci. 2008;274:68-75.

34. Rudick RA, Polman CH. Current approaches to the identification and management of breakthrough disease in patients with multiple sclerosis. Lancet Neurol. 2009;8:545-59.

35. Derfuss T. Personalized medicine in multiple sclerosis: hope or reality? BMC Med. 2012;10:116.

36. Coyle PK. Switching therapies in multiple sclerosis. CNS Drugs. 2013;27:239-47.

37. Karussis D et al. A recommended treatment algorithm in relapsing multiple sclerosis: report of an international consensus meeting. Eur J Neurol. 2006;13:61-71.

38. Freedman MS et al. Long-term safety and efficacy of teriflunomide in patients with relapsing forms of multiple sclerosis in the TEMSO extension trial. ACTRIMS. 2013;P544.

39. Confavreux C et al. Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. Mult Scler. 2012;18:1278-89.

40. Aubagio: Summary of product characteristics.

41. Gold R, Wolinsky JS. Pathophysiology of multiple sclerosis and the place of teriflunomide. Acta Neurol Scand. 2011;124:75-84.

42. Confavreux C et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13:247-56.

43. Vermersch P et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler. 2014;20:705-16.

44. Bar-Or A et al. Teriflunomide effect on immune response to influenza vaccine in patients with multiple sclerosis. Neurology. 2013;81:552-8.

45. Bar-Or A et al. Immune response to neoantigen and recall antigens in healthy subjects receiving teriflunomide. 2013;P622.

46. Vollmer T. Teriflunomide in routine clinical practice: design of the Teri-Pro study.

2013;DX58. CMSC Fifth Cooperative Metting. 30 May 2013.

47. Menguy-Vacheron F et al. Exploring the impact of teriflunomide on immune cells in patients with relapsing multiple sclerosis: design of the Teri-Dynamic study. ENS. 2013;P533.

48. Chitnis T. Immunological Insights into Pediatric MS. CMSC Annual Meeting. 2014.

49. Miller AE et al. TOPIC main outcomes: efficacy and safety of once-daily oral teriflunomide in patients with clinically isolated syndrome. ECTRIMS Congress. 2013.

50. Macdonell R et al. Teriflunomide reduces relapse-related sequelae, severe relapses, hospitalisations and corticosteroid use: pooled data from the phase 3 TEMSO and TOWER studies. ECTRIMS. 2013;P1095.

51. Leist TP et al. Pooled safety data from four placebo-controlled teriflunomide studies. AAN. 2014;P2.203.

52. Singer B et al. Frequency of infections during treatment with teriflunomide: pooled data from three placebo-controlled teriflunomide studies. AAN. 2013;P01.171.

53. Jung Henson L et al. Updated Pregnancy Outcomes in Patients and Partners of Patients in the Teriflunomide Clinical Trial Program. American Academy of Neurology. 2014;P4.161.

54. Miller A et al. Rapid elimination procedure of teriflunomide with cholestyramine or activated charcoal. Poster presentation. ACTRIMS. 2012;P10.

55. Hu Y et al. Investigation of the mechanism of action of alemtuzumab in a human CD52 transgenic mouse model. Immunology. 2009;128:260-70.

56. Lemtrada. Summary of product characteristics.

57. Kovarova I et al. Alemtuzumab pharmacokinetics and pharmacodynamics in comparison of Alemtuzumab and Rebif® efficacy in multiple sclerosis. ENS. 2012;P341.

58. Turner MJ et al. Immune status following alemtuzumab treatment in human CD52 transgenic mice. J Neuroimmunol. 2013;261:29-36.

59. Cox AL et al. Lymphocyte homeostasis following therapeutic lymphocyte depletion in multiple sclerosis. Eur J Immunol. 2005;35:3332-42.

60. Hartung H-P et al. Lymphocyte subset dynamics following alemtuzumab treatment in the CARE-MS I study. ECTRIMS. 2012;P935.

61. Coles AJ et al. The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. J Neurol. 2006;253:98-108.

62. Coles AJ et al. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. Ann Neurol. 1999;46:296-304.

63. Coles AJ et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008;359:1786-801.

64. Coles AJ et al. Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 clinical trial. Neurology. 2012;78:1069-78.

65. Fox E et al. Durable efficacy of alemtuzumab in relapsing-remitting multiple sclerosis patients who participated in the CARE-MS studies: three year follow-up. AAN. 2013;S41.001.

66. Twyman C et al. Relapse outcomes with alemtuzumab vs IFNB-1a in active relapsing-remitting multiple sclerosis patients who experienced disease activity while on prior therapy (CARE-MS II). AAN. 2013;P07.098.

67. Kieseier BC et al. Alemtuzumab has similar efficacy and safety in active relapsing-remitting multiple sclerosis (RRMS) patients who were treatment-naive or who relapsed on prior therapy. AAN. 2014;P2.209.

68. Arnold DL et al. Effect of alemtuzumab vs. Rebif® on brain MRI measurements: results of CARE-MS I, a phase 3 study. AAN. 2012;S11.006.

69. Arnold DL et al. Effect of alemtuzumab vs. Rebif® on brain MRI measurements. ECTRIMS. 2012;P877.

70. Giovannoni G et al. Disease activity-free status in comparison of alemtuzumab and Rebif® efficacy in multiple sclerosis I (CARE-MS I) phase 3 study. ENS. 2012;O288.

71. Hartung H-P et al. Alemtuzumab

reduces MS disease activity in active relapsing-remitting multiple sclerosis patients who had disease activity on prior therapy. AAN. 2013;P07.093.

72. Gupta A et al. Alemtuzumab improves quality of life compared to SC IFNB-1A in CARE-MS I. CMSC Annual Meeting. 2012;DX40.

73. Arroyo R et al. Alemtuzumab improves quality of life compared to SC IFNB-1a in CARE-MS II. ENS. 2013;P531.

74. Tuohy O et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. J Neurol Neurosurg Psychiatry. 2014;doi:10.1136/jnnp-2014-307721.

75. Havrdova E et al. Infection risk with alemtuzumab in patients with relapsing-remitting multiple sclerosis: pooled results from the CARE-MS I and II trials. ECTRIMS. 2013;P603.

76. Lycke J et al. Adverse event profile of alemtuzumab in active relapsing remitting multiple sclerosis patients who participated in the CARE-MS studies: three-year follow-up. ECTRIMS. 2013;P1053.

77. Coles AJ et al. Efficacy and safety results from comparison of alemtuzumab and Rebif® efficacy in multiple sclerosis I (CARE-MS I): a phase 3 study in relapsing-remitting treatment-naïve patients. AAN. 2012;S01.006.

78. LaGanke CC et al. Adverse event profile of alemtuzumab over time in active relapsing-remitting multiple sclerosis patients who experienced disease activity while on prior therapy (CARE-MS II). AAN. 2013;P01.174.

79. Twyman CL et al. Thyroid autoimmune adverse events in patients treated with alemtuzumab for relapsing-remitting multiple sclerosis: four-year follow-up of the CARE-MS studies. AAN. 2014;P2.199.