Clinical outcome measures in progressive multiple sclerosis

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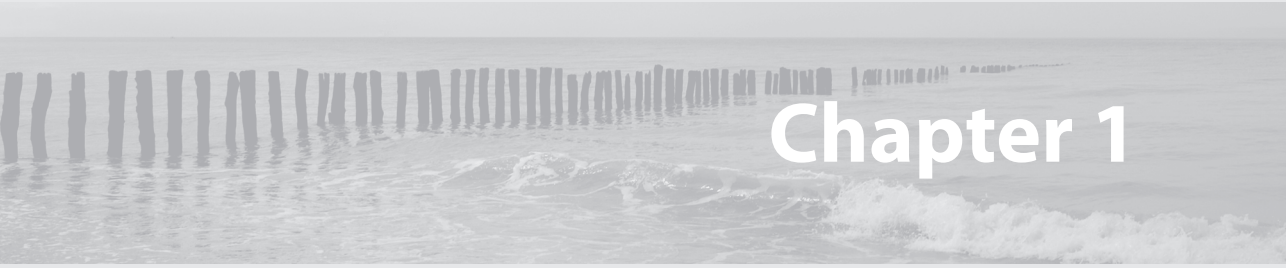

Chapter 1

Introduction

1.1 GENERAL INTRODUCTION ON MULTIPLE SCLEROSIS

Epidemiology

Multiple Sclerosis (MS) is a chronic, primarily inflammatory, demyelinating disease of the brain and spinal cord (central nervous system). It is potentially the most common cause of neurological disability in young adults. The clinical course is rather heterogeneous, just as the clinical manifestations. Worldwide, approximately 2.5 million people are estimated to be affected by MS with a largely varying prevalence, being highest in Northern Europe and North America: approximately 1 per 1000 inhabitants.[1-3] This uneven geographic distribution depends on an interplay between environmental exposure and genetic susceptibility, with an age-linked susceptibility to exposure. The role of environmental factors is among other things supported by changes in risk that occur with migration of people. There is a latitude gradient, meaning a higher incidence of MS at higher latitudes, which is possibly due to vitamin D deficiency. Further, there is evidence that certain virus infections, especially infection with the Epstein-Barr virus (EBV), pose a risk factor for MS.[4,5] At last, there is evidence that smokers may have a higher risk of MS, and there is suggestive evidence that smoking might adversely affect MS progression.[6]

Clinical presentation

The disease typically presents with an acute episode of neurological dysfunction (relapse). The most frequently involved neurological systems are the optic nerve (unilateral painful loss of vision), brainstem/posterior fossa (limb incoordination and gait ataxia, nystagmus, ophthalmoplegias, dysarthria), cerebrum/spinal cord (cognitive impairment, sensory and motor symptoms: paresthesia, hypesthesia and muscle weakness, bladder dysfunction, constipation, erectile impotence) and others such as pain and fatigue. Additional symptoms characteristic of demyelination are Lhermitte's sign (electric tingles running down one's back or limbs on neck flexion) and Uhthoff's phenomenon (appearance or aggravation of symptoms during heat or exercise).

The proportion of patients presenting as mentioned above is approximately 80%. These patients are classified as the relapsing-remitting (RR) subtype. Patients experience recurrent relapses with partial or complete recovery (remission). Eventually persistent symptoms accumulate and the majority of all relapsing-onset patients (approximately 80%) enters the secondary progressive phase, then classified as secondary progressive (SP). SPMS is characterised by steady progression of disability, with or without superimposed relapses. At last, in approximately 20%

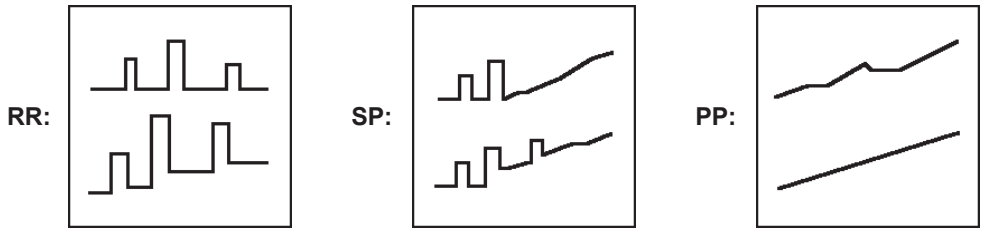

Figure 1.1 Schematic figure of MS subtypes, based on course of disease.
The X-axis represents time, the Y-axis represents neurological disability. RR: relapsing-remitting, SP: secondary progressive, PP: primary progressive.

of patients the disease is slowly progressive from symptom onset (primary progressive, PP). In these patients there is continuous accumulation of neurological disability without relapses or remissions, however mild fluctuations can occur (**Figure 1.1**).[2,7,8] In both SP and PP situations, progression starts at around 40 years of age.[9] Both progressive subtypes are characterised by predominantly spinal symptoms. Overall in MS, life expectancy is at least 25 years from disease onset with most patients dying from unrelated causes, or secondary infections due to advanced neurological disabilities, particularly of skin, chest and bladder.[1]

Diagnosis

The diagnosis of MS is based on demonstration of dissemination in space and in time, indicating different episodes affecting separate sites within the central nervous system. Specific diagnostic criteria are formulated for this purpose, which have been revised several times the past few years due to new evidence and consensus. Those criteria are based on clinical findings (symptoms and signs), with additional paraclinical evidence, such as cerebrospinal fluid (CSF) and Magnetic Resonance Imaging (MRI). The need for these paraclinical investigations depends on the available clinical information. Purely clinical dissemination in space is accomplished when there is objective evidence of 2 or more clinical lesions. Concerning CSF investigation, the presence of oligoclonal IgG bands or an increased IgG index is supportive ('positive CSF'). Concerning MRI, dissemination in space can be demonstrated by the presence of at least one T2 lesion, in at least two locations considered characteristic for MS (infratentorial, juxtacortical, periventricular and spinal cord). Dissemination in time based on MRI findings can be demonstrated by a new T2 lesion and/or gadolinium enhancing lesion(s) on follow-up MRI, or simultaneous presence of both gadolinium-enhancing and non-enhancing lesions at any time. It is imperative that alternative diagnoses are considered and excluded.[10-12]

Treatment

The aim of treatment in MS is to reduce the frequency and limit the lasting effects of relapses, prevent disability arising from disease progression, relieve symptoms, and promote tissue repair. At present, not all these goals have been successfully achieved, and unfortunately treatment is not yet available for patients at all stages of disease. However, several disease-modifying therapies (DMT) are available that have been shown to suppress disease activity and partially slow disease progression (in relapsing forms of MS). The longest known and most widely used drugs are interferon-beta and glatiramer acetate. Both reduce relapse rate with around 30% on average.[13-17] A more recent and more effective drug is natalizumab, a monoclonal antibody, which reduces relapse rate with approximately 60%. Due to – rare but – adverse safety features it is reserved as a second-line therapy for patients with highly active RRMS.[18] Other second line drugs include mitoxantrone and the latest developed, first orally administered drug fingolimod. Fingolimod prevents lymphocytes from migrating to the central nervous system. It is a promising new agent with approximately 50% reduction in relapse rate and around 30% reduction of disability progression. However, also this drug has some unfavourable safety issues. Therefore it is reserved for patients with highly active RRMS only.[19]

Concerning SPMS: patients transitioning from RR to SPMS and those with superimposed relapses may respond to interferon-beta therapy. Patients who are progressing rapidly, especially if there are superimposed relapses or there is MRI evidence of active inflammatory disease, may stabilize with mitoxantrone therapy.[20] There are no current roles for glatiramer acetate, natalizumab or fingolimod in the treatment of SPMS. Regarding PPMS, to date there are no approved disease-modifying treatments that slow the disease course. A double-blind placebo-controlled trial with glatiramer acetate[21] and small exploratory trials with interferon agents[22,23] failed to demonstrate efficacy in PPMS patients. Currently fingolimod is being evaluated for effectiveness in delaying disability progression in patients with PPMS.

At last, MS symptoms can be treated. In case of a relapse, intravenous methylprednisolone can be given. This has been demonstrated to have short-term beneficial effect on the speed of functional recovery, however it has no impact on (long-term) progression of the disease. Several drugs are available to decrease fatigue, painful spasms, erectile dysfunction and bladder problems.

In short, existent disease modifying therapies reduce the frequency of relapses but do not reverse existing deficits, and effects on the long-term accumulation of disability and disease progression are uncertain. While treatment options for early and relapsing forms of MS are numerous and have shown increased effectiveness, it is about time to find an effective therapy for progressive MS, the group of patients that still lack effective treatment options. After

this group of patients was initially neglected considering MS therapeutics, and subsequently therapeutic trials were organised but failed, there is currently an urgent need for trials with therapeutic agents that possess not only immunomodulatory, but additional neuroprotective and/or reparative properties, and that are of tailored design with outcome measures pre-eminently sensitive for disability.

1.2 CLINICAL OUTCOME MEASURES IN MULTIPLE SCLEROSIS

Disease activity and disease progression can be evaluated on the basis of different disease-specific clinical measures that assess and quantify impairment, disability, handicap and impact of MS. These important aspects of the disease can be assessed in various ways, from different viewpoints. For example from the doctor's perspective, by performing neurological examinations or functional tests, rather objective. Or more subjective, from the patient's perspective, by taking interviews or asking patients to complete questionnaires. The use of clinical outcome measures in MS is important, at the individual level and at the group level. At the individual level, clinical scales can be used as part of routine clinical care: to monitor the patient's disease course and, if possible, to assist in predicting the short-term and long-term disease course. This largely remains a future challenge. Also, the use of clinical scales at the individual level allows physicians to classify patients according to their level of disability. At the group level, clinical scales can be used also to register the disease course as part of natural history studies. Further, maybe most important, to evaluate response to experimental treatment in randomized clinical trials.

An ideal measurement instrument should be reliable (show consistent performance on the test items, measure in a reproducible fashion), valid (the scale measures what is intended), responsive (the scale is able to detect clinical change, largely important in clinical trials), clinically useful and meaningful (the scale is easy to use, understand and interpret, it applies to a wide range of patients and it measures aspects of the disease that are important to the patients).[24]

Challenges of clinical outcome measurement in MS

It is difficult to quantify neurological disability in a group of MS patients. The heterogeneity of not only the symptoms and signs, but also of the disease course with relapses, remissions, times of clinical stability or continuous slow progression, makes precise clinical measurement of MS disease activity complicated. There is a large variability between patients, but also within patients there can be a large variability over time.

Clinical scales used in the MS Center of VUmc Amsterdam

In our MS Center a large cohort of MS patients is prospectively followed up by structural clinical measurements as part of a health status assessment program designed to improve individual patient care. Disease-specific clinical outcome measures that are regularly used in this context are the following:

EDSS

The majority of studies focusing on the natural history of MS or evaluating experimental treatment effects in clinical trials have used the Expanded Disability Status Scale (EDSS)[25] to measure disease severity. The EDSS is an ordinal scale ranging from 0 (normal) to 10 (death due to MS), with steps of 0.5 points. A higher score on the scale indicates a higher disability level. It involves a standardised, extensive neurological examination, some questions on often occurring disease symptoms, and – if possible – walking a required distance to determine the maximum walking distance. On the basis of this information a score is being given on each of 7 neurological Functional Systems (FS: visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, cerebral functions). Then, in combination with the ambulation status, those FS scores are translated into the EDSS-score, according to a circumscribed system. EDSS scores below 4.0 refer to patients who are fully ambulatory (able to walk ≥ 500 meters), the precise step is defined by the FS scores. EDSS scores between 4.0 and 5.0 are defined by both the FS scores and the walking range. EDSS scores of 5.5 to 8.0 are exclusively defined by the ability to ambulate and type of assistance required, or the necessity to use a wheelchair. Patients with EDSS scores above 8.0 are essentially restricted to bed and now arm function, communication and eating/swallowing define the score. So despite its name, the EDSS is not a scale of disability alone, but actually of impairment in its lower range, of disability in its middle range and of handicap in its upper range. In the **Appendix**, the complete scale is shown.

Currently, the EDSS is still the gold standard to rate disability in MS, despite well known psychometric disadvantages: it is an ordinal scale, with steps that are non-linear and great emphasis on mobility status at the cost of other important aspects of disability (e.g. cognition, vision). It is limited in its ability to reflect change in neurological status, especially at certain levels sensitivity to change is poor (in more severely ill patients). Reliability is limited. It does not incorporate the patient's perspective.[24,26,27] Also, it is quite time-consuming to perform and requires a great deal of experience in neurology and MS in particular. Despite these limitations, it has been the basis of clinical outcome measurement in MS for years, and most physicians are familiar with the clinical meaning of the scale.

MSFC

The Multiple Sclerosis Functional Composite (MSFC)[28] is a functional measure that includes 3 quantitative, continuous tests. The Timed 25-Foot Walk (T25FW) evaluates ambulation by measuring the time needed to walk 25 feet (7.62 meters) as quickly as possible. The 9-Hole Peg Test (9HPT) evaluates arm dexterity by measuring the time needed to insert 9 pegs in a board with 9 holes and subsequently remove them one at a time as quickly as possible. Both the dominant and the non-dominant hand are tested. The fastest time of two trials of the T25FW and 9HPT is used. The Paced Auditory Serial Addition Test (PASAT) evaluates cognition by presenting serial numbers on a CD (a single digit every 3 seconds) that need to be added to the previous digit and each time the sum should be named by the patient. The total number of correct answers is counted. If patients are unable to perform one of the tests due to MS-related symptoms, the maximum allowed time (180 seconds for T25FW and 300 seconds for 9HPT) or the minimum score (0 for PASAT) for this test is assigned.[29,30] When the MSFC is administered for the first time, all 3 tests are practised at least once before baseline assessments are performed. To create the composite MSFC-score, the actual scores on the 3 tests are transformed, Z-scores of the different component scores are created and eventually summed to an overall composite score.

The MSFC was originally proposed to address shortcomings of the EDSS, but is has not yet gained wide acceptance, mainly because it is hard to understand the clinical relevance of the scores and their changes over time. At present, significant change (worsening or improvement) of the MSFC-score remains to be defined. It is not evident from the total score which component contributes most to the total score. Changes on the different components in different directions combined into a total MSFC score could bottom out the total change, or distort the outcome and mask for example differential treatment effects on arm and leg function. Therefore mean changes from baseline in the composite score might not be a reliable assessment of treatment effects in clinical studies, and other ways are sought, for example investigating the separate components. It is easier to interpret test results if one can directly link them to a specific function, like walking function or arm function. However also on the separate components, changes need to be further investigated in order to define clinically relevant change. Research has been done to address this question. In the studies described in this thesis, we most frequently used the T25FW and 9HPT. In some studies we left out the PASAT, because of unfavourable properties of this test, including evident practice effects. Concerns have been raised about the use of the PASAT as the cognitive component of the MSFC, and research has been done to replace the PASAT by other tests measuring cognition.[31]

Despite these drawbacks, the MSFC (and its separate components) indeed approaches some shortcomings of the EDSS. Strengths are the fact that the MSFC can be administered by a trained technician rather than a neurologist, it is simple to administer regardless of prior experience and it can be performed in 15-20 minutes. The scales are continuous, quantitative and in consequence have improved sensitivity to change.

GNDS

The past few years, increased attention is paid to the patient's perspective, among others by regulatory authorities providing guidelines to evaluate therapeutic effectiveness in MS. In line with this, more patient-based outcome measures were developed. The Guy's Neurological Disability Scale (GNDS)[32] is an interview-based questionnaire measuring disability in MS from the patient's perspective, with items including cognition, mood, vision, speech, swallowing, upper limb function, lower limb function, bladder function, bowel function, sexual function, fatigue and 'others'. Each subcategory of the GNDS is scored separately ranging from 0 (normal) to 5 (maximal help required), leading to the GNDS sum score (range 0-60). This questionnaire based on patient self-report can be applied by any health care worker. Advantages of this scale are the incorporation of the patient's point of view and the fact that it is user-friendly and capable of comprising a large range of disabilities seen in the MS population. However, the fact that the interviewer has to interpret the patient's answers and translate them into a certain score is a disadvantage of the scale. Please see the **Appendix** for the complete questionnaire.

MSIS-29

The Multiple Sclerosis Impact Scale (MSIS-29)[33] is another patient-based measure. It is a questionnaire measuring disease impact of MS on daily life, that is completed by the patient him/herself. It can be divided into two subscales: a physical scale (MSIS Physical) consisting of 20 items and a psychological scale (MSIS Psychological) with 9 items. The range of scores is 1 (no impact on daily life) to 5 (extremely influencing daily life). Two separate scores for the subscales are calculated and converted to a 0-100 scale.[34] The Physical and Psychological scale should be looked at separately because combining them could mask important information on physical and psychological health. In this thesis we mainly focused on the Physical scale. The greatest strength of the MSIS-29 is that it is a patient-reported measure, without interference of an investigator or physician. The scale was developed from an item pool generated on the basis of interview with MS patients, using a psychometric approach. It is an easy instrument

to administer, it can be completed at the patient's home in case the patient is not able to visit the hospital and it is of use in the full range of impairments, disabilities and handicaps seen in MS patients. Also, it is related to other measures of disease progression.[35] In the **Appendix** the complete MSIS-29 questionnaire is shown.

MSWS-12

The Multiple Sclerosis Walking Scale (MSWS-12)[36] is the most recently developed patient-based measure in MS, and is a self-rated measure of walking ability. Walking ability is a relevant and commonly used measure of disease impact in patients with MS, given that walking limitations are highly prevalent with a large majority of patients experiencing some degree of ambulatory disability.[33,37] Moreover, difficulty walking is one of the greatest concerns for MS patients.[38] The MSWS-12 comprises a 12-item scale, ranging from 1 (no problems with walking at all) to 5 (extremely difficult). As with the MSIS-29, the total score is converted to a 0-100 scale.[34] In our MS Center, the MSWS-12 has only recently been included in the series of structural clinical measurements. The entire MSWS-12 questionnaire is shown in the **Appendix**.

1.3 AIMS AND OUTLINE OF THIS THESIS

There is an urgent need for effective therapy in the progressive phase of MS. In the long term, a vast majority of all MS patients experiences progressive disease. To find a possible treatment effect of experimental therapy, clinical trials in progressive MS should be carefully designed with well-chosen endpoints. The choice of clinical trial endpoints is a complex evolution of expected effect size, expected number of events and other factors. Options of clinical trial endpoints vary between the different subtypes of MS, and were initially better explored in relapsing MS, while the progressive forms of disease were more or less excluded from therapeutic trials. For example in RRMS one can count the annual relapse rate and MRI measures generally show distinct inflammatory activity, whereas in PPMS the clinical course is without relapses and MRI activity is strikingly less.[39] Also, clinical trials are very strenuous for patients with a higher level of disability. For reliable measurement of slowly accumulating disability, the customary time course of clinical trials is already relatively short. This trial duration should be kept as short as possible to reduce trial load and drop-out rates, which are relatively high in progressive MS.[40] However, to be able to detect possible treatment effects, the outcome measure must be sensitive enough to measure disease progression in the control group within this time course.

Altogether, trial design in progressive MS poses certain challenges. The aim of this thesis was to enlarge insight into clinical disease progression in order to improve clinical outcomes in progressive MS and to support trial design. At the same time we hoped to contribute to improved prediction of future disease course and impact at the individual level.

Because of the above mentioned challenges, there is a longstanding controversy on the optimal approach to measuring disease severity and disease progression in MS, and on the best outcome measures for evaluating the impact of DMT. In this thesis we searched for responsive and meaningful long-term outcomes that are suitable for progressive MS. To facilitate trial design in progressive MS further investigation of clinical scales in this phase of the disease is crucial, to see which scales are responsive and which short-term changes on different scales predict future clinically important outcome. Regulatory authorities require endpoints that adequately reflect the true clinical condition of patients, and not some surrogate measure that may not reach the level of patient awareness. The intended treatment effect should impact the clinical experience of patients. Objectivity is obviously important in ascertaining indisputable treatment effects, but the patient perspective should not be left out. It is crucial to consider the (long-term) experienced disease impact and disease burden.

Concerning the psychometric properties of the clinical scales described in this thesis: we performed studies with different existing clinical scales of which in general reliability and validity were already examined. In our studies we mainly focused on the (relative) responsiveness and clinical meaningfulness of the scales. Because we specifically focussed on disease progression, all studies were of longitudinal study design.

Chapter 2 describes our search for ways to determine clinical disease progression: responsiveness and cut-off points for significant change in primary progressive MS. In **chapter 2.1** we investigated which scale – or combination of scales – is most responsive in PPMS. We included the EDSS and both extremity motor function tests of the MSFC, the T25FW and 9HPT. In **chapter 2.2** we looked at deterioration and improvement on the three separate components of the MSFC in PPMS. We also looked at the ratio of improved versus progressed patients, the signal-to-noise ratio, in order to determine the optimal cut-off for significant change, in addition to results of earlier studies. A PPMS-population forms an ideal study population to examine disease progression. There is no confounding influence of relapses and remissions. In theory there should be no improvement, only slowly progressive deterioration which is a good situation to examine responsiveness and to reliably determine cut-offs indicating disease progression. The follow-up duration of the two studies described in this chapter was 2 years.

In chapter 3 we investigated how different commonly applied scales compare in predicting future clinically important outcome in progressive MS. We explored the relation between the relatively short-term changes which are generally under investigation in trials, and the long-term outcome of patients. In order to indicate which scales are most worthwhile to look at in the long term and hence particularly clinically meaningful in progressive MS. In **chapter 3.1** we investigated associations between short-term changes on different scales and long-term outcome of disability as rated by the EDSS. We used the EDSS as outcome in this study because despite its well-known limitations, it is still the widely known and accepted outcome measure for the rating of disability in MS. We included change on the EDSS, T25FW, 9HPT and GNDS. The mean total follow-up duration of this study was 7.5 years. In **chapter 3.2** we investigated associations between short-term changes in physician-rated measurements (EDSS, T25FW and 9HPT) and long-term impact according to two patient-reported outcome (PRO) measures, the MSIS-29 and MSWS-12. The mean total follow-up duration was 8.4 years. In this study we decided to measure the long-term outcome by impact, instead of by disability (EDSS), because walking ability might not be the best aspect to measure in order to classify and distinguish patients in progressive MS. Although it certainly is an important aspect of disability to be evaluated, in the progressive phase of MS the majority of patients is in the disease stage where ambulation impairment dominates the EDSS score. Another concern is the fact that the EDSS is non-linear. Therefore in this study we decided to focus on the patient-reported impact in the long term. Both studies were performed on the basis of a cohort of progressive MS patients (PP/SP) in order to render progression on the different scales plausible. In the SPMS patients, none of the assessments were obtained during or within three months of a possible relapse, to rule out distorting influence of relapses and remissions.

Finally, in chapter 4 we investigated which clinical domains contribute most to disease impact as reported by the patient in progressive MS. In this chapter we investigated how changes in potential outcome measures relate to increased disease impact, by using the MSIS-29 as an anchor measure, in order to determine which clinical domains contribute most to increased disease impact. In addition, we studied patients in whom the observed changes in potential outcome measures and MSIS-29 Physical were concordant or in fact not matching. For this purpose we investigated long-term (4 to 6 years) changes on the MSIS-29, EDSS, T25FW, 9HPT and GNDS, in a cohort of progressive MS patients (PP/SP).

REFERENCES

1. Compston A, Coles A. Multiple sclerosis. Lancet 2002; 359: 1221-1231.
2. Compston A, Coles A. Multiple sclerosis. Lancet 2008; 372: 1502-1517.
3. Coles A. Multiple sclerosis. Pract Neurol 2009; 9: 118-126.
4. Ascherio A, Munger K. Epidemiology of multiple sclerosis: from risk factors to prevention. Semin Neurol 2008; 28: 17-28.
5. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol 2007; 61: 288-299.
6. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. Ann Neurol 2007; 61: 504-513.
7. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996; 46: 907-911.
8. Kremenchutzky M, Rice GP, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. Brain 2006; 129: 584-594.
9. Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis. Brain 2006; 129: 595-605.
10. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001; 50: 121-127.
11. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005; 58: 840-846.
12. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011; 69: 292-302.
13. 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: 655-661.
14. 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: 1498-1504.
15. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 1996; 39: 285-294.
16. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995; 45: 1268-1276.
17. Paty DW, Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. Neurology 1993; 43: 662-667.

18. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006; 354: 899-910.

19. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010; 362: 387-401.

20. Hartung HP, Gonsette R, Konig N, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet 2002; 360: 2018-2025.

21. Wolinsky JS, Narayana PA, O'Connor P, et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol 2007; 61: 14-24.

22. Leary SM, Miller DH, Stevenson VL, Brex PA, Chard DT, Thompson AJ. Interferon beta-1a in primary progressive MS: an exploratory, randomized, controlled trial. Neurology 2003; 60: 44-51.

23. Montalban X. Overview of European pilot study of interferon beta-Ib in primary progressive multiple sclerosis. Mult Scler 2004; 10 Suppl 1: S62-S64.

24. Thompson AJ, Hobart JC. Multiple sclerosis: assessment of disability and disability scales. J Neurol 1998; 245: 189-196.

25. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33: 1444-1452.

26. Sharrack B, Hughes RA, Soudain S, Dunn G. The psychometric properties of clinical rating scales used in multiple sclerosis. Brain 1999; 122: 141-159.

27. Hobart J, Freeman J, Thompson A. Kurtzke scales revisited: the application of psychometric methods to clinical intuition. Brain 2000; 123: 1027-1040.

28. Cutter GR, Baier ML, Rudick RA, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 1999; 122: 871-882.

29. Hoogervorst EL, Zwemmer JN, Jelles B, Polman CH, Uitdehaag BM. Multiple Sclerosis Impact Scale (MSIS-29): relation to established measures of impairment and disability. Mult Scler 2004; 10: 569-574.

30. Kalkers NF, de Groot V, Lazeron RH, et al. MS functional composite: relation to disease phenotype and disability strata. Neurology 2000; 54: 1233-1239.

31. Drake A, Weinstock-Guttman B, Morrow S, Hojnacki D, Munschauer F, Benedict R. Psychometrics and normative data for the Multiple Sclerosis Functional Composite: replacing the PASAT with the Symbol Digit Modalities Test. Mult Scler 2010; 16: 228-237.

32. Sharrack B, Hughes RA. The Guy's Neurological Disability Scale (GNDS): a new disability measure for multiple sclerosis. Mult Scler 1999; 5: 223-233.

33. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain 2001; 124: 962-973.

34. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome. Health Technol Assess 2004; 8:iii, 1-iii,48.

35. McGuigan C, Hutchinson M. The multiple sclerosis impact scale (MSIS-29) is a reliable and sensitive measure. J Neurol Neurosurg Psychiatry 2004; 75: 266-269.

36. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). Neurology 2003; 60: 31-36.

37. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain 2010; 133: 1914-1929.

38. Heesen C, Bohm J, Reich C, Kasper J, Goebel M, Gold SM. Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. Mult Scler 2008; 14: 988-991.

39. Thompson AJ, Kermode AG, MacManus DG, et al. Patterns of disease activity in multiple sclerosis: clinical and magnetic resonance imaging study. BMJ 1990; 300: 631-634.

40. Neilley LK, Goodin DS, Goodkin DE, Hauser SL. Side effect profile of interferon beta-1b in MS: results of an open label trial. Neurology 1996; 46: 552-554.