

Summary thesis Jolijn Kragt

‘Measuring disease progression in MS: do patients’ and physicians’ perspectives match?’

Multiple sclerosis (MS) is a chronic progressive neurological disease, characterized by an inflammatory, demyelinating (loss of myelin around nerves) and neurodegenerative process of the brain and spinal cord. The average age of onset of symptoms is 30 years, and more women than men develop the disease. Patients experience a wide variety of clinical signs and symptoms: visual dysfunction, muscle weakness, sensory deficits, impaired coordination of hand and leg movements, bladder and bowel dysfunction, cognitive problems, mood impairment and fatigue. Different subtypes of MS can be distinguished: relapsing-remitting (RR-) MS with relapses (or exacerbations/ attacks) and remissions, secondary-progressive (SP-) MS with a slow progressive disease course after a period with relapses and remissions, and primary-progressive (PP-) MS which is a subtype without relapses/remissions.

A way to evaluate disease progression is making use of disease-specific clinical measures designed to assess impairment, disability and impact of MS. These clinical measures can either be patient-derived, such as quality of life-questionnaires, or physician-based, for example the physical neurological examination. On the one hand, clinical measures can be used for routine clinical care, by trying to predict short- and long-term disease course of individual patients. On the other hand, these measures are being applied in groups of patients to monitor response to experimental treatment in randomized clinical trials.

In order to choose the best available clinical measure, one has to judge the quality of candidate measures. Three properties of clinical measures are important: reliability (the degree to which a measure is free of random error), validity (does an outcome measure target and measure what it is intended to measure?) and responsiveness (the ability to detect change in the construct over time, i.e. 'sensitivity to change'). Finally, one should always take into account the clinical meaningfulness of a clinical measure: what does the outcome assessed by a certain measure tell us about the patient, and has it indeed any value for the patient him/herself?

In the MS center Amsterdam, four different clinical outcome measures have been applied, ranging from patient-derived to physician-based measures, to a high number of MS patients, over a long period of time, as part of a health status assessment program designed to improve individual patient care. Besides examining the patient him/herself, we retrieved valuable information from proxies, e.g. partners of patients, on the impact of disease on daily life of the patient. We applied the Multiple Sclerosis Functional Composite (MSFC), which combines the results of three quantitative tests: the Timed 25-foot Walk (T25FW), a test of the ambulatory function of the patients, the 9-hole Peg Test (9HPT) that assesses upper limb function, and the Paced Auditory Serial Addition Test (PASAT) that examines aspects of cognitive function. Furthermore, we used the Expanded Disability Status Scale (EDSS), a standardized neurological examination, based on scoring of seven neurological functional systems combined with the ambulatory status of the patient. The Guy's Neurological Disability Scale (GNDS) is a patient-based interview by which means 12 functional domains are evaluated. Finally, our MS patients

filled in the Multiple Sclerosis Impact Scale (MSIS-29), that assesses the physical and psychological impact of MS on daily life.

In our first study (**chapter 2**), a pilot study on bladder dysfunction in MS, the importance of the different perspectives (patient versus physician) became apparent. Urinary symptoms (bowel/bladder Functional System score of the EDSS and bladder dysfunction score of the GNDS) were correlated to an objective measurement of bladder dysfunction (post micturition residual volume). We found substantial differences between the views of patients and physicians. In the group of patients that did *not* report having urinary symptoms, approximately 12 % had a residual of ≥ 100 ml and 4 % a residual of ≥ 200 ml. Therefore, the subjective assessments were of no value for predicting the presence of a clinically relevant postvoiding volume. These findings suggested that patients and physicians could also diverge in their opinions on other aspects of disease progression in MS, and that particularly these differences might be interesting to explore.

Therefore, the aim of this thesis was to examine disease progression, from a patient-derived as well as a physician-based perspective, in a broad spectrum of studies. We hypothesized that, in order to get a complete and detailed analysis of disease progression in MS patients over time, the use of various clinical outcome measures, both patient-derived and physician-based, are needed.

In **part 1** of this thesis the emphasis was on the physician-based perspective, with several chapters discussing data of some physician-based clinical outcome measures. In **chapter 3**, a commonly applied disability endpoint in MS clinical trials has been evaluated. The

clinically meaningful EDSS change has been defined as a change of 1.0 points in patients with an entry EDSS score of 5.5 or lower, or 0.5 point in patients with a higher EDSS score. In this study, we examined whether these changes can be considered as similar, by comparing these changes to changes on two other clinical measures, the GNDS and MSFC. Our results indicated that these changes can not be considered equal, since GNDS and MSFC changes were higher in the group of patients with baseline EDSS ≥ 6.0 than in patients with baseline EDSS ≤ 5.5 . **Chapter 4** depicted the assessment of the clinical meaning of changes on two quantitative tests of motor function, namely the T25FW and the 9HPT. This was accomplished by comparing 20 % changes on these measures to concomitant changes on the GNDS, a patient-derived interview on daily-life disability. Worsening on T25FW and 9HPT indeed had clinical impact on disability as perceived by MS patients during daily life functioning; we found that worsening on T25FW was mainly due to increase in perceived disability related to lower extremity function and fatigue; GNDS worsening associated with worsening on 9HPT was more diffuse with respect to domains involved. In **chapter 5**, we have studied the responsiveness and predictive value of the EDSS and MSFC, in patients with primary progressive MS. Over a period of two years, responsiveness was shown to be limited and mean changes were highly dependent on the baseline scores, both for EDSS and MSFC. The predictive value of short-term worsening (baseline to year 1) to predict subsequent worsening (year 1 to year 2) of neither EDSS nor MSFC was very powerful.

The patient-derived perspective was the central theme in **part 2** of this thesis, with chapters considering patient-derived clinical outcome measures. **Chapter 6** described the

clinimetric validation of the MSIS-29, a patient-derived questionnaire that measures the impact of MS on daily life, when completed by proxy respondents. Cognitive impairment and serious mood disturbances might interfere with consistent self-assessment, and, in such cases, proxies might provide valuable information. This study showed that the MSIS-29 could be used reliably in partners of patients with MS. These results created a solid basis for further use of MSIS-29 proxy measurements in MS. In **chapter 7**, the relation between data on proxy versus self-reports has been studied, focusing on factors that might affect agreement and discrepancies. Agreement between patients and partners was good for the physical scale of the MSIS-29, and slightly less but still adequate for the psychological scale. We concluded that partners might be useful sources of information when assessing the impact of MS on daily life of patients. Furthermore, we examined the responsiveness of two self-report questionnaires, the MSIS-29 and the Multiple Sclerosis Walking Scale (MSWS-12), by studying a group of patients before and after intravenous steroid treatment (**chapter 8**). As external criteria to distinguish improved patients from those who did not improve we used both a subjective score (transition question) and an objective examination score (the EDSS). The MSIS-29 and MSWS-12 proved to be responsive measures that were capable to detect group changes induced by treatment. However, it was difficult to distinguish differences between individual changes in patients.

Finally, in **part 3** of this thesis the patient-derived and physician-based perspectives were being combined, in order to find out on which issues patients and physicians agreed and on which they disagreed. **Chapter 9** described the interrelation of changes on the EDSS,

the 9HPT, the T25FW and the physical subscale of the MSIS-29 (MSIS-physical) and the concept of combining different scales. By studying the frequency of relevant worsening over time on various outcome measures, we showed the potential benefit of applying different outcome measures when assessing disease progression in MS. Especially adding a patient-derived measure to a physician-based measure most likely had a positive impact on sensitivity to change. However, combining different outcome measures revealed the phenomenon of ‘opposing changes’ (worsening on one measure while improving on any other measure). In **chapter 10** the relevance of the findings of this thesis are discussed and recommendations for future research are presented.

Based on the findings summarized above we concluded the following:

Some changes are only measured by physicians while patients do not notice them, and some changes are only experienced by patients themselves whereas physicians do not measure them. Patient-derived and physician-based clinical outcome measures give complementary information about different aspects of disease progression in MS and should therefore be used together. Recently, a new concept in measuring disease progression has been developed, combining endpoints of several measures in one composite. We would propose incorporating in a composite at least the EDSS, T25FW and MSIS-29. However, further research is needed to evaluate the optimal way to combine outcome measures before implementing this strategy in clinical studies or randomized clinical trials in MS.