



Chapter 5

Summary and general discussion

Difficulties in trial design in progressive MS, a group of patients without effective treatment options, urge us to closer study and improve clinical outcome measures in this phase of the disease. Therefore, in this thesis, we studied reliable measurement of slowly accumulating disability. We tried to find the optimal approach for measuring disease severity and progression, which is crucial to evaluate the impact of DMT. In the studies described in chapter 2 we investigated changes in a PPMS population over a relatively short follow-up period of two years. The studies described in chapters 3 and 4 provide longitudinal data on a cohort of progressive MS patients (PP and SP) over a longer follow-up period, varying from 4 to 10 years.

DISCUSSION OF OUR FINDINGS

Finding ways to determine clinical disease progression: responsiveness and cut-off points for significant change in primary progressive MS

Chapter 2.1 focuses on the selection of clinical scales sensitive to gradual disease progression. We compared event rates on the EDSS, T25FW and 9HPT, and on different combinations of these scales, to see whether we could define an endpoint that has a higher event rate than the EDSS alone. We looked at the T25FW and 9HPT as separate MSFC-components, and used predefined changes instead of mean change scores, because we wanted the endpoint to be clinically interpretable and applicable. The concept of combining changes on different outcome measures in order to increase responsiveness was introduced in this study. We combined worsening on either T25FW or 9HPT with worsening on the EDSS, while another study combined all three components of the MSFC,¹ in order to make the use of MSFC data more clinically meaningful. The idea is that each of the component events alone must reflect a significant change in the patient's clinical condition and is therefore clinically meaningful. In that case any worsening on the composite endpoint will imply a clinically meaningful event.

The T25FW had the highest event rate on the separate scales, independent of the baseline disability level. The concept of combining changes on different scales introduced a new phenomenon: the existence of opposing changes: worsening on one measure while improving on the other at the same time. This phenomenon is not completely unexpected since different scales assess different clinical dimensions of the disease. However, in PPMS, real improvement over 1 or 2 years is unlikely to occur and can thus be considered as “noise”. In our study population, over 2 years, rates of clinically meaningful improvement and opposing changes were clearly lower than at 1 year, whereas rates of worsening were clearly higher. Therefore, considering

the ratio of “signal-to-noise” in this study, a term of 2 years seems much more meaningful to observe in PPMS than 1 year. At the decisive time point of 2 years, the combination of T25FW and EDSS had the highest event rate. Also this combination seemed most consistent considering the amount of improvement picked up. Therefore, the conclusion of this study was the introduction of “*worsening on either T25FW or EDSS*” as the most appropriate composite endpoint. Different properties of T25FW and EDSS lead to different selections of worsened patients and consequently enlarge the chance of detecting disease progression. A combination of the two measures apparently gives complementary information in PPMS. The 9HPT could also complement the EDSS by including assessment of important clinical aspects of disability not adequately captured by the EDSS alone, however the event rate on this scale is by far not as high as on the T25FW in this PPMS population.

Trying to make the use of MSFC data more clinically meaningful, by defining meaningful endpoints of functional decline, the question rises what is the optimal cut-off point for reliable and clinically meaningful change on the MSFC components? In previous studies, a 20% change on the T25FW and 9HPT was considered to reliably indicate a true change in function² and also seemed to be associated with a change in patient perceived disability, and is therefore clinically meaningful.³⁻⁵ For the PASAT, no cut-off points have been defined. More recent, a 15% change of the MSFC was introduced.¹ In chapter 2.2, we looked at deterioration and improvement on the three separate components of the MSFC (T25FW, 9HPT and PASAT) and we tried to answer the question which cut-off point is sensitive enough to measure progression without incorporating too much noise, by considering the “signal-to-noise” ratio. For the T25FW and 9HPT, we could confirm the previously suggested cut-off of 20%. For the PASAT we were not able to determine a reasonable cut-off point. We could only conclude that the PASAT is not very suitable to use as a test to identify disease progression in a PPMS population, amongst others because of the large amount of observed improvement.

We can summarize that using the separate MSFC-components instead of the composite MSFC-score has indeed made the use of MSFC data more clinically meaningful, with available cut-offs for reliable and clinically meaningful change assessed in several studies.²⁻⁶ With the exception of the PASAT. For the PASAT there is no appropriate cut-off available and doubts about the usefulness of this test are prevalent, not only in progressive MS but also in general.⁷ We therefore left out the PASAT in our following studies. However, the T25FW and 9HPT are applicable tests, whether or not combined with EDSS data, and especially the T25FW is responsive in PPMS.

How do different commonly applied scales compare in predicting future clinically important outcome in progressive MS?

In chapter 3 we explored the relation between several relatively short-term changes which are frequently under investigation in trials, and the long-term outcome of patients. To facilitate trial design in progressive MS, predicting future clinically important disability by means of short-term changes on different clinical scales is crucial. Are the changes that are used on a large scale in trials indeed associated with the long-term clinical state? In chapter 3.1 we focussed on the long-term outcome of disability as rated by the EDSS, still the gold standard in clinical outcome measurement in MS. Comparing early change on EDSS, T25FW, 9HPT and GNDS in their relation to the long-term outcome of disability, we found that both early change on EDSS and T25FW predict long-term EDSS with comparable strength. Concerning early EDSS change, this may be expected. Next to this, T25FW change was the only predictor significantly improving prediction when added to early EDSS change in the prediction model. We support the use of early T25FW examinations in future clinical trials in progressive MS, given that this test is not only easy to administer (easier than the EDSS), but it also adds significant independent prognostic information. Other early changes did not significantly improve prediction of long-term disability, neither alone nor combined.

The ordinal nature of the EDSS complicates the use of this scale as outcome variable in a prediction model, which is a limitation of the study described in chapter 3.1. Besides, in the progressive phase the vast majority of patients is in the disease stage where ambulation impairment dominates the EDSS score, which makes it hard to distinguish patients. More information is needed on the long-term outcome of patients according to themselves. How large is the experienced disease impact on health and functioning, and how does this impact vary between patients? Few studies have addressed these questions so far, whereas more and more attention has been drawn to the facts that MS is a disease that affects the entirety of who the patient is and that assessments should be made of the overall effect of therapies on the patient as a whole.^{8,9} Before measurement of treatment effects in a patient-centered way can be implemented in clinical trials, we need more information on the relation between patient-reported measures and the more conventional, physician-rated measures. How do the well-known, commonly applied clinical scales compare in their quality to predict future disease impact? We know that patients' and physicians' perspectives sometimes differ since they measure different clinical aspects of MS.¹⁰ But can physician-rated assessments predict the patient's long term impact of disease?

To answer those questions, in the study described in chapter 3.2 we chose to focus on the long-term impact according to two patient-reported outcome (PRO) measures that reflect

patient-perceived impact of disease, the MSIS-29 and MSWS-12. We studied the relation between short-term changes in physician-rated measurements (EDSS, T25FW, 9HPT) and the long-term outcome according to those PRO measures. We found that early changes on physician-rated scales have long-term impact at a group level. Especially early T25FW change, rather than EDSS change, was associated with long-term reported impact. Early change in T25FW was the only physician-rated change significantly related to the experienced physical impact after at least five years. Further, early T25FW change was significantly related to subsequently experienced walking-limitations. Even early change in 9HPT was significantly associated with long-term walking-limitations, whereas early EDSS change only showed an association with long-term walking-limitations in one-to-one comparison of the different groups. This is remarkable, given that walking-limitations are widely represented by the EDSS, and the T25FW and 9HPT are in fact more objective than the EDSS. Intuitively, one would expect more objective measurements to be less related to the subjective assessment. On the other hand, the quality of the measurement of the MSFC components compared to the measurement of the EDSS could be the very reason why associations with reported long-term impact were more apparent for the T25FW and 9HPT than for the EDSS: much more standardized and precise, so that changes have a better signal-to-noise ratio. Furthermore, due to the ordinal and non-linear nature of the EDSS and relatively long “staying times” at the higher EDSS levels, the T25FW is more responsive to changes than the EDSS in progressive MS patients (in a certain range of disability levels). Those aspects could very well influence associations between short-term changes and the long-term reported impact. This study for the first time provides longitudinal data that show that short-term changes in physician-rated outcomes, especially T25FW and to a lesser extent 9HPT and EDSS, are associated with long-term patient-perceived walking ability and global disease impact, in progressive MS. This knowledge could well be of use in a trial design for progressive MS. Associations were observed at the group level. Because of large variability in short-term changes, unfortunately our observations can not be directly used to predict disease impact in individual patients with sufficient reliability. This study was rather a first step to investigate whether there are associations between short-term physician-rated changes and long-term patient-reported impact and which scales are particularly associated with the long-term impact. The next step would be to investigate the predictive value of short-term changes at the group level and eventually at the individual level, in order to respond to the patients’ need of reliable predictions of their future disease course. Currently this remains a major future challenge. The results of this study are supportive of the use of objective, physician-rated scales in clinical trials in progressive MS, of which particularly the T25FW seems promising.

Detecting clinically relevant changes in progressive MS

In chapter 4 we further explored the relation between patient-reported measures and the more conventional physician-rated measures. We investigated how changes in potential outcome measures relate to increased disease impact, by using the MSIS-29 as an anchor measure. In addition, we studied patients in whom the observed changes in potential outcome measures and MSIS-29 Physical were not matching. Associations between continuous changes and event rates on EDSS, T25FW, 9HPT and GNDS were compared in relation to significant MSIS-worsening. Change in the GNDS contributed most to disease impact as reported by the patient. The spinal-plus subscale of the GNDS clearly dominates the GNDS sum score in this progressive MS population. Also change in T25FW contributed largely to the experienced disease impact. Compared to the EDSS (and 9HPT), the relation between T25FW and patient-perceived impact seems to be stronger. This finding, that an objective test as the T25FW has such a good relation to change in the patient-perceived disease impact, is remarkable. At the same time it supports the use of T25FW examinations in clinical trials in progressive MS, in combination with the earlier described results. Finally, our results suggested a trend of less increase in disease-impact in patients with higher baseline impact and disability and longer disease duration, possibly due to a response shift phenomenon accompanying the MSIS-29 Physical scale. Our results suggested specific profiles of change in T25FW and MSIS-29. In the higher disability range, a subgroup of patients showed distinct physical worsening according to substantial T25FW deterioration, while they did not report an increase in disease impact. This specific subgroup of patients does not exist in the lower to moderate disability range, where the impact of MS is considered higher, and possibly aspects like acceptance of the diagnosis and developing coping strategies play a larger role, that decreases over time. This phenomenon may have implications for patient selection in trials for progressive MS.

CONCLUSIONS

Of all different clinical scales we investigated in this thesis, the T25FW seems the most promising scale for use in clinical trials in progressive MS. It has shown to be responsive in progressive MS, most distinct of all clinical scales when considered separately (according to event rates described in chapter 2.1 and chapter 4). Its reliability is relatively good compared to the 9HPT and PASAT, considering the amount of “noise” measured and the “signal-to-noise” ratio in a purely progressive MS population (chapter 2.2). In addition, early change on the scale is significantly related to long-term disability (chapter 3.1) and to the long-term disease impact experienced by the patient, concerning the global physical impact as well as walking

limitations (chapter 3.2). At last, change in the T25FW contributes substantially to increase in disease impact (chapter 4).

However, a combination of T25FW examinations with other scales is still preferable, in order to provide additional information capturing different clinical aspects of the disease and different perspectives (physician-based vs patient-based), to further increase responsiveness and thus the likelihood to detect a real worsening of function, and in order to further outline the clinical state. For example, T25FW examinations combined with the EDSS, because the EDSS is helpful to classify patients according to their level of disability and characterize a patient population at a glance, given the fact that its clinical meaning is familiar with all clinicians and MS researchers. In this respect, the T25FW can not yet replace the EDSS as the gold standard. Also, we have seen that a combination of T25FW and EDSS increases responsiveness. Whereas for example a combination of T25FW and MSIS-29 (Physical scale) is valuable as well, because in this way also the patient's perspective is included. Depending on what a specific clinical setting requires, different scales should be combined, in order to make outcome measurement more tailored. Because different scales have their own specific limitations, dependent on the situation (e.g., patient population, stage of the disease) the best of different scales should be combined.

In short, based on the results described in this thesis, we think that the T25FW should be included in outcome measurement in progressive MS *in any case*, preferably in combination with other clinical scales. The use of the T25FW, 9HPT and PASAT as separate scales instead of combined into a total MSFC-score has improved insight into the clinical meaning of the changes and has simplified interpretation of the test results. However, there are also some limitations concerning the T25FW that should be mentioned. In patients with higher levels of disability, who are still able to walk but have serious walking limitations, the test may be burdensome or even risky. Further, there is a (obvious) ceiling effect when the stage is reached the patient can not walk anymore and the maximum score of 180 seconds is given. At this stage the T25FW can thus not worsen anymore and other measures are needed to discriminate differences in clinical state between patients. For example the more subjective measures like MSIS-29 and/or MSWS-12; although the T25FW cannot worsen anymore, the experienced impact will still vary between patients. On the other hand, there can be a floor effect as well, in patients with mild disease. In this case, a longer walking test could have better precision in discriminating differences in disability, for example the 6-minute Walk Test (6mWT).¹¹ In addition, in the patients with relatively mild disease, there is more noise, and it is important to make use of cut-off values to indicate clinically relevant deterioration. These ceiling and floor effects are also present in the other MSFC-components, the 9HPT and PASAT.

The MSIS-29 however, has small floor and ceiling effects, which is an advantage of the MSIS-29. Moreover, the fact that the MSIS-29 would especially be sensitive to change in the more disabled patients¹² makes it well applicable for progressive MS. Other advantages are that both physical and psychological scales have low correlations with age, sex and disease duration, indicating that they are not biased by these variables.¹³ Additional attractive aspects are the methodology in which the patient's perspective is incorporated, being developed from and completed by patients. This last aspect is a strength of the MSIS-29 compared to the GNDS, since items for the GNDS were developed through expert clinical opinion rather than on the basis of interviews with people with MS.¹⁴ Finally, the response shift phenomenon, which was suggested by the results of chapter 4 but also in earlier studies,¹² is an intrinsic and unavoidable aspect of self-report measures in general, that forms a possible limitation of the MSIS-29. Still, altogether the MSIS-29, at least the physical scale, is a suitable and useful measure to assess disease impact of MS on daily life in a wide range of patients, including the progressive patients. The psychological scale of the MSIS-29 needs to be examined in more detail to determine its usefulness as an outcome measure in progressive MS, since this was not addressed in this thesis.

CLINICAL IMPLICATIONS

We have investigated the EDSS, T25FW, 9HPT, GNDS, MSIS-29 and MSWS-12 in this thesis, some scales more extensive than others. Based on this research and on personal experience in using these scales, recommendations for their application in different clinical settings are summarized in **Table 5.1**. The listed choices are personal suggestions, and additional experience as well as future research results are needed to further elucidate those recommendations, in order to form a dynamic guide to the use of clinical scales in different clinical settings in MS.

Concerning prediction of disease progression at the individual level, our studies showed too much variability on the scales to make reliable predictions on an individual basis. The greater part of our results were found at a group level. The T25FW might not only be promising for use in clinical trials, but possibly also to predict the individual patient's disease course. This needs to be confirmed in complementary studies though, in order to give concrete recommendations.

RECOMMENDATIONS FOR FUTURE RESEARCH

First of all, it would be important to replicate our results in different, independent cohorts. Ideally, with larger numbers of patients and maybe even longer follow-up duration. In progressive MS though, this is not very easy to accomplish and there is always a trade-off

Table 5.1 Recommendations for the application of the clinical scales investigated in this thesis in different clinical settings

Clinical setting	Recommended scales	Commentary
Routine clinical care, Recently diagnosed MS	1. EDSS	• Extensive familiarity with clinical meaning, practical to classify and characterize patients.
	2. MSIS-29	• Including patient's perspective next to doctor's perspective. Impact is often high in early MS due to accepting diagnosis, learning coping strategies.
Routine clinical care, Long disease duration	1. EDSS	• Extensive familiarity with clinical meaning, practical to classify and characterize patients.
	2. MSIS-29	• Including patient's perspective next to doctor's perspective. Impact is important to discriminate differences between patients with long disease duration.
	3. MSWS-12	• Walking function is an important aspect in patients with long disease duration.
Clinical trial proof of concept, DMT (progressive MS)	1. EDSS 2. T25FW	• Due to different properties this combination gives complementary information and increases responsiveness.
Clinical trial phase III, DMT (progressive MS)	1. EDSS	• Due to different properties this combination gives complementary information and increases responsiveness.
	2. T25FW	
	3. MSIS-29	• Including patient's perspective next to doctor's perspective is important because of possible discrepancies between physical worsening and reported impact.

between a long follow-up duration and increased drop-out of disabled patients who are less able to come to the hospital. Further, as already mentioned above, future studies should focus more specific on improved prediction of disability and disease impact at the individual level, in order to guide patient consultation and therapeutic decisions. In addition, we need to further study in which way exactly our study results can be incorporated in trial design. When for example T25FW and EDSS are used as a composite endpoint (“*worsening on either T25FW or EDSS*”), one should be aware of the possibility of – undesired – opposing changes. However, when the requirement for sustained change is fulfilled, possible noise in the endpoint (resulting from transient changes or measurement imprecision) is eliminated, and the likelihood that the event corresponds to irreversible increase in disability enlarges. This is an important recommendation for future studies, since in our studies we were not able to fulfil this requirement, mainly because we did not use trial cohorts but cohorts of patients who were prospectively followed up by

regular, yearly visits. Because of the importance of comprehensible interpretation of clinical outcome measures and based on the results of our and previous studies, we would suggest the incorporation of specifically defined optimal cut-off values rather than continuous data in trial design.

The determination of those optimal cut-off values should be further evaluated for the MSIS-29, both the physical and the psychological scale. For the physical scale, there has only been one study investigating significant change, where a change of 8 points or more was defined as clinically significant using the EDSS as an anchor measure.¹² This should be further evaluated and confirmed in additional, independent cohorts. Significant change on the psychological scale has not been studied so far. Also, the determination of significant change on the GNDS should be further evaluated. A change of at least 3 points in the sum score has been postulated, but doubts have been expressed that this might be too small a difference to be really significant.¹⁴⁻¹⁶ The complementary study of those specific optimal cut-off values should be extended to the MSWS-12 as well. Because the MSWS-12 was implemented in the health status assessment program of our MS Center only quite recently, we have not yet been able to analyse this scale longitudinally. Evaluation of its responsiveness and identification of clinically meaningful change would be relevant for future studies with regard to trial design in progressive MS. An optimal cut-off value for clinically relevant change on the MSWS-12 has not been published so far. Preliminary data suggest a 6-point change as threshold for clinically meaningful change.¹⁷

The advantage of composite endpoints is that different components can be exchanged and with this different dimensions can be added, depending on the clinical situation. In this thesis we focussed on the EDSS, MSFC, GNDS, MSIS-29 and MSWS-12, but of course there are many more disease specific scales worthwhile to further investigate concerning their possible role in outcome research in (progressive) MS. In this respect, some recommendations regarding future studies could be the following. First, the replacement of the PASAT by another measure of cognition that is less susceptible to practice effects, for example the Symbol Digit Modalities Test (SDMT).⁷ In most of our studies we left out the PASAT because of concerns regarding this specific test, but cognitive function itself could be an important outcome in progressive MS. Additional research is needed to study the possible role of cognition in outcome measurement in progressive MS, as well as the impact of cognition on patient-based outcome measures. Second, addition of a spasticity scale, like for example the Multiple Sclerosis Spasticity Scale (MSSS-88),¹⁸ could be valuable for outcome measurement in progressive MS, since spasticity is a very common symptom in patients with MS and a major contributor to disability, particularly in progressive MS. Third, addition of a visual test could be useful, not pre-eminently for progressive MS, but maybe more applicable to early RRMS. For example contrast letter acuity.¹⁹ At last,

considering the current focus on patient-based outcome measurement, additional measures of quality of life could be valuable in outcome measurement in progressive MS, for example the Functional Index for Living with Multiple Sclerosis (FILMS).²⁰

Of course these other potentially additional components should have proven responsiveness, validity and reliability. Above mentioned recommendations are suggestions, meant to illustrate how composite clinical endpoints can be adjusted for populations with varying (disability) profiles. One could also go one step further, by adding other than clinical measures to the composite endpoint. For example the relation between the T25FW or MSIS-29 and different MRI measures of disease could be explored in more detail in future studies, and could well be of relevance to trial design for progressive MS. This is however outside the scope of this thesis, in which we have focussed on the clinical outcome measures in progressive MS.

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