Multiple Sclerosis and Related Disorders 44 (2020) 102242

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

The transitional phase of multiple sclerosis: Characterization and conceptual framework

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ARTICLE INFO

Keywords:
Progressive multiple sclerosis
Disease course
Biomarker
Disease modifying therapy
Trial design

ABSTRACT

The conversion of relapsing-remitting multiple sclerosis (RRMS) to secondary progressive MS (SPMS) cannot be defined by a sharp threshold determined by event-based measures, but rather represents a gradual process. In consequence, there may exist a transitional phase between RRMS and clearly established SPMS. So far, transitional MS has been poorly characterized in terms of patient properties, course of disease and therapeutic interventions that may delay conversion to SPMS. Furthermore, the pathogenesis of transitional MS is incompletely understood, and no definitive imaging or laboratory test informs when exactly a patient has entered the transitional MS phase. Here we review the current knowledge and evidence characterizing the transitional phase of MS and propose potential designs and criteria for a prospective clinical study in patients with transitional MS.

1. Introduction

Multiple sclerosis (MS) is characterized by highly heterogeneous disease courses in individual patients that may represent a continuum of gradually different disease phenotypes. With the exception of primary progressive MS (PPMS), most patients experience an initial phase dominantly characterized by recurrent relapses (RRMS). Their symptoms are fully or partially reversible and may contribute to accumulation of disability. In parallel, clinicians may observe disability progression independent of relapse activity (PIRA) which gradually takes over, thus resulting in secondary progressive MS (SPMS). A period of gradual conversion between RRMS and SPMS, i.e. a “transitional” phase of MS, is supposed to exist. While a number of published therapeutic studies have included patients with relapsing MS, a term that comprises RRMS and SPMS with superimposed relapses, no clinical studies have been performed that specifically address the transitional phase of the disease so far.

Abbreviations: 9HPT, 9-hole peg test; BVMT-R, brief visuospatial memory test-revised; CGI, clinical global impression; CHI3L1, chitinase-3-like protein 1; CNS, central nervous system; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FSMC, fatigue scale for motor and cognitive functions; FSS, functional systems scale; GCIPL, combined ganglion cell and inner plexiform layer; GFAP, glial fibrillary acid protein; HADS, hospital anxiety and depression Scale; LCSLC, low contrast Sloan letter chart; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSIS-29, multiple sclerosis impact scale-29; MSFC, multiple sclerosis functional composite; NfL, neurofilament light chain; OCT, optical coherence tomography; PASAT, paced auditory serial addition test; PIRA, progression independent of relapse activity; PPMS, primary progressive multiple sclerosis; pRNFL, peripapillary retinal nerve fiber layer; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SDMT, symbol digit modalities test; SF-36, short form 36; SPMS, secondary progressive multiple sclerosis; TREM-2, triggering receptor expressed on myeloid cells-2; T25FW, timed 25-foot walk; 2MWT, 2-minutes walking test; TUG, timed up and go test

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https://doi.org/10.1016/j.msard.2020.102242
Received 1 March 2020; Received in revised form 17 May 2020; Accepted 24 May 2020
Available online 29 May 2020

2. Disease progression in MS

2.1. Classification of MS stages

In the 2013 update of the MS disease classification, disease activity as measured by clinical relapses, new or enhancing lesions on brain or spinal cord magnetic resonance imaging (MRI), or ongoing progression of disability were introduced as modifiers of the two core MS phenotypes, relapsing-remitting (RRMS) and progressive MS (PPMS, SPMS) (Lublin et al., 2014). Generally, differences between phenotypes are rather qualitative than quantitative, often precluding sharp delineations. Clinically, progressive MS and as such SPMS is defined by the accumulation of disability without relation to relapses as opposed to relapse-associated worsening, which may be fully or partially reversible.

Progressive MS is defined as a steadily increasing, objectively documented neurological dysfunction or disability without unequivocal recovery, while fluctuations and phases of stability, superimposed relapses and MRI activity may occur. The predominant sign of SPMS is increasing motor dysfunction, independently from relapse-associated deterioration. While this may be influenced operationally by the use of the EDSS in the definition of SPMS, it is consistent with the concept of a neurodegenerative length-dependent axonopathy as a central component of progressive MS (Giovannoni et al., 2017).

2.2. Clinical predictors of conversion to SPMS

According to natural history studies, 30-50% of untreated RRMS patients convert to SPMS within 10-15 years after disease onset, while 80% reach the progressive stage at 20 years (Weinshenker et al., 1989). Data from observational studies in more contemporary cohorts have suggested a shift towards a slower progression rate and conversion to SPMS (Tremlett et al., 2006, Tedeholm et al., 2013). A low percentage of patients will never convert to SPMS and may represent a group with so-called “benign” MS (Skoog et al., 2012). Based on a large sample of patients with 5 years follow-up after progression, the following criteria for an early diagnosis of SPMS were identified (Lorscheider et al., 2016): EDSS $\geq$4.0, pyramidal FSS $\geq$2, disability progression confirmed after $\geq$3 months by 1.0 (previous EDSS $\leq$5.5) or by 0.5 points (previous EDSS $\geq$6.0). Clinical predictors of an earlier transition to SPMS remain controversial and may include male sex, older age at MS onset, higher number of relapses early in disease course, poor recovery from first (Confavreux et al., 2003) and subsequent relapses (Novotna et al., 2015), overall MS disease duration (Scalfari et al., 2014) and early treatment with injectable therapies versus highly effective immunomodulatory drugs during the RRMS phase (Brown et al., 2019).

While higher age at RRMS onset is a predictor of a shorter latency to SPMS, patients with younger age at onset still develop SPMS earlier in their life. Males convert to SPMS more rapidly than women (mean difference: 4 years) and are younger at conversion to SPMS (mean difference: 3 years). Males and females reach an EDSS of 8.0 at the same mean age (Tremlett et al., 2008). Motor and/or sphincter symptoms at MS onset were identified as dominant predictors of SPMS (Bergamaschi et al., 2007, Bergamaschi et al., 2015). Moreover, a more rapid disability trajectory is associated with an increased risk of SPMS (Fambiatos et al., 2019). To predict the risk of conversion to SPMS, a nomogram employing gender, calendar year of birth, first-recorded EDSS, age at the first EDSS evaluation and age at disease onset was constructed (Manouchehrinia et al., 2019).

Worsening of ambulation, cognition, balance, muscle strength, visual symptoms, bladder symptoms and fatigue were identified by patients and physicians to be related to the transition from RRMS to early SPMS (Ziemssen et al., 2019). However, no specific symptom definitively indicated progression to SPMS for the individual patient.

3. The concept and clinical assessment of transitional MS

As the conversion to SPMS cannot be defined as a sharp threshold defined by event-based measures but rather takes place as a gradual process, there may exist an interim period of several years duration between RRMS and clearly established SPMS. Currently, SPMS represents a retrospective diagnosis. Clinically, “transitional MS” is a prequel of SPMS with signs of incipient progression during a variable duration of time before SPMS is unequivocally diagnosed. In a study involving 123 MS patients, the mean duration of diagnostic uncertainty between RRMS and SPMS was 2.9 years, and in 70% of the cases, the diagnosis of SPMS was only established when an EDSS of $\geq$6.0 was reached (Katz Sand, 2015).

The inability to more precisely capture the onset of SPMS may in part be due to the limitations inherent to the EDSS itself which include: non-linear characteristics with the shortest timespan spent in the range of 3.0–5.0, emphasis on lower limb motor function, low sensitivity to cognitive and upper limb changes in advanced MS, high inter-rater variability, particularly in the lower ranges of the scale (1.0–3.5), and partly subjective evaluation (bowel and bladder function, ambulation). Of note, an EDSS increase confirmed at 3- and 6-month intervals overestimates the percentage of patients with permanent increase in disability (at 5 years) by 30% and 26%, respectively (Kalincik et al., 2015). Thus, a preferable instrument for clinical assessment may be the well-standardized MSFC (the z-score of 9HPT (hand function), 25-foot Walk (ambulation) and PASAT3 (cognition), which is based entirely on objective components, and shows high intra- and inter-rater reliability. A deterioration by 0.5 points in the total score or by 20% in the single components can predict subsequent EDSS change (Cohen et al., 2000). The use of MSFC in longitudinal studies is impeded by repetition effects of the PASAT (Solari et al., 2005), which may be mitigated by replacing it with the SDMT that also has shown a higher sensitivity. Thus, the modified MSFC, which may allow for more sensitive detection of cognitive decline and upper extremity motor dysfunction, may be a preferable composite instrument of tracking progression versus EDSS (López-Góngora et al., 2015).

Operationally, transitional MS may be defined as confirmed MSFC progression in a relapse-free interval independent of EDSS progression. However, the following questions would have to be answered: can a meaningful change in the modified MSFC (total score or components) confirmed after a predefined time period (e.g. 6 months) predict the subsequent conversion to SPMS better than the EDSS or despite a stable EDSS value?

Novel rater-independent measuring tools (e.g. based on sensor technologies and mobile applications) allow for continuous objective monitoring of patient mobility, gait patterns, action range, dexterity, sleep patterns and selected cognitive functions in daily life. As an example, Flachenecker et al. (Flachenecker et al., 2019) used sensor-based gait analysis to support the clinical assessment of walking abnormalities and identified stride length at the individual maximum speed as a sensitive discriminator. These tools may thus provide sensitive early indicators of ongoing relapse-independent progression and could be integrated in the definition of study endpoints in transitional MS.

4. Diagnostic findings associated with transitional MS

4.1. Cognition and fatigue

In general, cognitive problems are increasingly prevalent in MS over time (Achiron et al., 2013, Kister and Bacon, 2013) and over the stages from onset to RRMS to SPMS (Potagas et al., 2008). Moderate-to-severe fatigue and lower grade depression show an increase with disease duration (). Yet, some patients are able to withstand a considerable disease burden without significant cognitive impairment, an observation that underlines the concept of cognitive reserve (Santangelo et al.,

2019). Studies on specific cognitive and neuropsychiatric impairments applicable to the transitional phase of MS are virtually absent. In a first attempt to identify potential cognitive profiles related to disease stages, a study form the Netherlands compared RRMS, SPMS and PPMS (Huijbregts et al., 2004). When controlling for age and gender, it turned out that overall RRMS patients performed cognitively better than the progressive group. However, RRMS patients performed worse than matched healthy control subjects, with processing speed, visual memory and executive function showing significant performance differences.

These findings indicate that cognitive profiling according to disease courses obviously poses a challenge since the target cognitive domains are already affected in RRMS patients and just increasing in severity over time. With respect to the transitional phase, it is of interest that SPMS patients differed from RRMS patients most significantly in visuospatial short-term memory and learning. This may be regarded as the most sensitive cognitive change parameter to discriminate between RRMS and SPMS but also between SPMS and PPMS, as confirmed by recent data (Renner et al., 2020).

4.2. CNS pathology

Neuropathologically, no abrupt change in phenotype is observed when patients enter the progressive phase of MS. White and grey matter lesions as well as neuroaxonal degeneration evolve continuously (Stadelmann et al., 2019, Schirmer et al., 2011). In line with fewer enhancing lesions in MRI and less relapses, macrophage-rich actively demyelinating lesions become increasingly rare with time (Frischer et al., 2015). An exhaustion of neuronal compensatory mechanisms may be linked to the time point when disease progression becomes clinically apparent. In contrast to later stages of disease, in transitional MS, many lesions may still show signs of macrophage activation, demyelination, and axonal damage at the lesion edge, and thus active ongoing pathology which is potentially amenable to therapeutic intervention (Faissner et al., 2019).

4.3. Magnetic resonance imaging characteristics

MRI is the most important surrogate marker to monitor MS disease activity, but no standardized imaging measures of progressive MS are currently established. Conventional MRI parameters (number/load of T2 and gadolinium-enhancing lesion) appear to be unable to predict the risk of conversion to SPMS (Manouchehrinia et al., 2019). Still, early focal inflammatory disease activity and spinal cord lesions may represent predictors of very long-term disease outcomes (over 15 years) in RRMS (Brownlee et al., 2019). Cortical lesions that may be found even in early MS display both numerical and volumetric increase with disease evolution from RRMS towards SPMS. The cortical lesion volume correlates with increasing EDSS and more severe cognitive impairment (Roosendaal et al., 2009). Long-term longitudinal studies found a higher number and volume of cortical lesions, early loss of cortical thickness and loss of cerebellar cortical volume as significant predictors of a conversion to SPMS (Scalfari et al., 2018). As a novel marker, atrophy of existing lesions may be more common in progressive MS than in RRMS (Dwyer et al., 2018). In a longitudinal study over 4 years, gray matter atrophy was a predictor of progression, while white matter atrophy was unrelated (Fisher et al., 2008). Along that line, spinal cord gray matter atrophy may also represent an early marker of SPMS (Schlaeger et al., 2014). The progressive disease course was significantly associated with a reduced spinal cord area independent of the spinal cord lesion number. According to a model of disease evolution (Leray et al., 2010, Rocca et al., 2002), RRMS is dominated by white matter pathology, while gray matter damage is compensated by remyelination and plasticity. As these mechanisms become exhausted, gray matter pathology takes over (Roosendaal et al., 2009, Calabrese et al., 2013), inducing a gradual transition towards irreversibly progressive disability, i.e. SPMS. In transitional MS, intermediate imaging findings should be expected. Higher numbers of new and enlarging cortical lesions, incipient gray matter and cortical atrophy as well as atrophied lesions may provide indicators of transitional MS. The development and validation of an MRI score to measure changes typical for transitional MS is an obvious, but still challenging approach to detect early secondary progression.

4.4. Biomarkers

Biomarkers identifying MS patients at risk of conversion to SPMS, would be highly useful if they enable early intervention with the potential of better long-term outcomes. Preferred candidates include markers of axonal destruction and intracerebral inflammation. Ideally, these would be serum markers easily accessible by blood sampling. However, levels of CNS target molecules in blood are often very low down to the femtomolar range, requiring highly sensitive techniques, e.g. single molecule array (SIMOA), for valid detection (Disanto et al., 2017).

Neurofilament light chain (NfL) is a cytoplasmic protein highly prevalent in myelinated axons (Gaetani et al., 2019). It is released in the cerebrospinal fluid (CSF) and blood upon axonal damage and has been under investigation as a disease marker in a number of neurodegenerative conditions. NfL serum levels have been shown to be elevated in SPMS versus RRMS patients prior to study treatment. Consistently, NfL levels show a modest positive correlation with change of EDSS over time and the rate of brain atrophy (Kuhle et al., 2017). However, NfL is not an inflammation-independent marker of neurodegeneration. While it proved to be highly sensitive, it is not specific for MS-related processes, and individual thresholds have not yet been prospectively determined.

Glial fibrillary acidic protein (GFAP) is the main astrocyte intermediary filament and upregulated during activation. In the CSF, GFAP is elevated in SPMS versus RRMS patients and correlates with EDSS. GFAP levels may predict the rate of EDSS worsening over 8 to 10 years (Linker et al., 2009, Malmeström et al., 2003). However, no evident information benefit was found versus NfL measured in serum. In the near future, also serum data on GFAP levels will become available via the SIMOA technique.

Chitinase 3-like I (CHI3L1) protein, which is secreted by activated macrophages, showed elevated levels in the CSF of patients with progressive MS in a moderate-sized cohort study (Cantó et al., 2015). Yet, CHI3L1, which can also be measured in serum, may prove useful as a marker of innate immune activation, a pathological hallmark of progressive MS. A recent article describes the combined elevation of CHI3L1 and NfL in CSF preceding diagnosis of clinical progression in RRMS patients, potentially identifying a subset of RRMS patients that may benefit from timely intervention (Gil-Perotin et al., 2019).

While a range of interesting biomarkers with promising data are under investigation, it should be noted that any predictive potential has essentially been shown on the population level rather than in individual patients. Thus, their usefulness for routine clinical purposes, particularly in transitional MS, remains to be established.

4.5. Retinal optic coherence tomography

Retinal optic coherence tomography (OCT) provides a simple non-invasive diagnostic procedure to analyze axonal and neuronal degeneration (Petzold et al., 2017). Recent studies have reproducibly shown on a group level that the peripapillary retinal nerve fiber layer (pRNFL) thickness (a measure of axonal degeneration) in eyes without optic neuritis correlates with MS disease duration, EDSS score, brain atrophy and cognitive impairment, while the combined ganglion cell inner plexiform layer (GCIPL) thickness (a measure of neuronal degeneration) correlates with EDSS and progression of disability (Petzold et al., 2017).

MS subtypes may be discriminated by pRNFL thickness in eyes

without prior optic neuritis, which tends to be more strongly reduced in patients with progressive MS. This finding may indicate that axonal loss is a more prominent feature of progressive versus relapsing MS (Bjartmar and Trapp, 2003). Moreover, optic neuritis-independent pRNFL and GCIPL thinning are prognostic markers for future EDSS progression (Martinez-Lapiscina et al., 2016, Knier et al., 2017, Zimmermann et al., 2018). In a recent study in patients with progressive MS, pRNFL was thinner in SPMS vs. PPMS. pRNFL evolution correlated with EDSS, and similar results were obtained for GCIPLGuerrieri, n.d. These results suggest a stronger involvement of the visual system in SPMS versus PPMS, while neurodegeneration appears to occur at the same rate in SPMS and PPMS.

The IMSVISUAL consortium investigated the potential of pRNFL thickness as a biomarker of disease progression in a large multicenter cohort (Martinez-Lapiscina et al., 2016). In patients with a pRNFL thickness of ≤88 μm the risk of disability worsening during 1-3 years of follow-up was doubled, with a further risk increase in the fourth and fifth year. In a cohort of early RRMS patients, those with baseline GCIPL volume of <2 mm^3 in the absence of optic neuritis had a more than six-fold increased risk of EDSS progression in the following three years (Knier et al., 2017). Since the predictive value of OCT has only been shown on the population and not on the individual level, the usefulness for routine clinical purposes, particularly in transitional MS, remains to be established.

5. Disease-modifying therapy to prevent progression

5.1. Are immunotherapies for the transitional phase of MS feasible?

The primary goal of any proposed treatment for patients in the transitional phase, is preventing, delaying or at least slowing the accumulation of disability. However, pathophysiological and clinical findings support the notion that the disease process becomes gradually less amenable to immunomodulatory drugs because of (i) the declining contribution of peripheral mechanisms of immune cell activation, (ii) the decrease of immune cell migration to the CNS, (iii) formation of lymphoid aggregates in the meninges, (iv) chronic microglia activation, and (v) accumulation of irreversible neurodegeneration.

Neurologists tend to continue ongoing immune therapies into the perceived transitional phase even though the relative efficacy of the available drugs has not been adequately studied in this stage and the risk-benefit ratio becomes less favorable. It has been shown that higher-efficacy immunotherapies (natalizumab, fingolimod, dimethyl fumarate, alemtuzumab, cladribine, rituximab and mitoxantrone) reduce the risk of disability outcomes in the EDSS 3-6, 4-6 and 6-6.5 epochs compared to lower-efficacy therapies or no therapy (Lizak et al., 2017). Interestingly these immunotherapies slowed progression also in patients with few relapses (median: 0 relapses in the 6-6.5 epoch), which gives a rationale for immunomodulation in transitional MS. Randomized controlled trials of immunotherapy specifically designed for the transitional phase of MS are currently lacking.

5.2. Lessons from studies in established progressive MS

Many studies that tested immune therapies in patients with definitive SPMS or PPMS failed to demonstrate clinically relevant efficacy. For most compounds, the observed effects are generally more pronounced in younger patients with remaining inflammatory disease activity as evidenced by contrast enhancing lesions on MRI or superimposed relapse activity (for overview on trials performed for individual substances, see Table 1).

As a common feature, these studies used time-to-event endpoints as their primary efficacy criteria, facilitating the detection of significant differences between treatment arms. However, the more meaningful question of the magnitude of long-term benefits achieved by these therapies remains to be answered. This may be achieved *post hoc* by

Table 1
Designs and results of placebo-controlled therapeutic studies in patients with progressive MS.

Drug	Condition	Main clinical result	Trials	Licensing status in progressive MS (EU)
Glatiramer acetate	SPMS	Trend to reduction of disability progression	Phase III PROMiSe (Wolinsky, 2004)	Not licensed
Natalizumab	SPMS	No reducedeed risk of EDSS and multicomponent progression Reduced 9HPT progression	Phase III ASCEND (Kapoor et al., 2018)	Not licensed
Interferon beta-1a/-1b	SPMS	Time to progression: 3 studies negative, 2 positive	Phase III European IFNB North-American IFNB SPECTRIMS (Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS (SPECTRIMS) Study Group 2001) IMPACT NORDIC	Approved for SPMS with relapses
Mitoxantrone	SPMS PMS	Reduction of disability progression Improvement in composite endpoint (5 clinical measures incl. EDSS, ambulation index, time to first treated relapse)	Phase III MITOX MIMS	Approved for highly active RRMS associated with rapidly evolving disability, in patients for whom no alternative treatments are available
Fingolimod	PPMS	No reduced risk of disability progression	Phase III INFORMS (Lublin et al., 2016)	Not licensed
Ocrelizumab	PPMS	Reduced risk of disability progression	Phase III ORATORIO (Montalban et al., 2017)	Approved for PPMS with signs of inflammatory activity
Siponimod	SPMS	Reduced risk of disability progression	Phase III EXPAND (Kappos et al., 2018)	Approved for SPMS with signs of inflammatory activity
Cladribine	RMS	Reduced risk of disability progression	Phase III CLARITY (Cook et al., 2011)	Approved for relapsing forms of MS with signs of inflammatory activity
Opicinumab	RRMS, SPMS	Primary endpoint missed (multicomponent endpoint)	Phase II SYNERGY (Cadavid et al., 2019)	Phase III trial ongoing
Ibudilast	PPMS, SPMS	MRI: reduced loss of brain parenchymal fraction	Phase II (Fox et al., 2018)	Phase III trial ongoing
Alpha lipoic acid	SPMS	Reduced loss of brain volume	Phase II (Spain, 2017)	Phase II trial ongoing
Simvastatin	SPMS	Improved SF-36 physical component	Phase II MS-STAT (Chan et al., 2017)	Not licensed

Table 2
Criteria and design for a putative prospective observational study in patients with transitional MS.

Patient baseline characteristics	
MS disease duration	≥ 4 years
Number of previous relapses	≥ 2
EDSS score	3.0 to 5.0
Relapse-independent increase of disability	EDSS increment of ≥0.5 points over the previous year or ≥1 point over the previous 2 years; both with confirmation after ≥ 3 months
Radiographic characteristics	≥1 of the following: ≥1 cortical lesion(s), evidence of cortical atrophy and/or smoldering lesions
Disease activity during previous 2 years	≥ 1 clinical relapse or ≥ 1 new or enlarging T2 lesion on MRI
Study procedures	
Duration of follow-up	≥ 3 years
Timing of clinical visits	At baseline, every 6 months and as clinically appropriate
Parameters to be documented at study visits[1]	
MS treatment(s)	Type, dosage, timing, duration
Disability status	Clinician global impression (CGI) Overall disability (EDSS) Hand-arm function (9HPT) Walking ability (T25FW, 2MWT, TUG) Cognition (SDMT, BVMT-R) Vision (LCSLC)
Neuropsychiatric aspects and quality of life	Fatigue (FSMC) Depression (HADS) MS specific quality of life (MSIS-29) General quality of life (SF-36)
Brain MR imaging	T2 hyperintense lesions Gadolinium-enhancing lesions T1 hypointense lesions Smoldering lesions Total brain volume Cortical volume Gray matter volume (cortical/subcortical) Connectivity parameters
Retinal OCT	pRNFL GCIPL
Molecular biomarkers in serum	NfL CHI3L1 GFAP

[1] Performed at baseline, every 6 months and as clinically appropriate.

responder analyses or by using continuous quantitative measures.

The absent or at best moderate effects of currently available therapies tested for progressive MS may indicate that patients were included too late in the process of transition to SPMS. This notion support efforts to (i) more timely identify patients at risk of progression, and (ii) investigate novel promising therapies in patients who are in the transitional phase before SPMS is unequivocally reached.

6. Proposed patient characteristics and endpoints of a prospective study in transitional MS

As transitional MS is not a sufficiently defined entity, an interventional study aiming specifically at this population appears currently unfeasible. A prospective observational clinical study should aim at gathering data that allow a more thorough characterization of transitional MS and estimate treatment effects of potentially promising therapies. The selection of patients eligible should aim at the exclusion of patients with early MS and pure RRMS on the one hand, and established progressive MS on the other. Criteria and design for a putative study in a transitional MS are summarized in Table 2.

7. Conclusion

While a range of drugs is available that quite effectively control the types of MS dominated by relapse activity, halting MS disability progression over the long-term disease course is the next challenge in MS therapy. So far, therapeutic trials in patients with established SPMS have shown disappointing or at best modest benefits. Therefore, preventing or delaying the conversion to SPMS during the transitional phase appears a worthwhile approach. Due to a different preponderance of immune-mediated mechanisms, study concepts involving immunotherapies should capture patients early in the transition.

Declaration of Competing Interest

IK received compensation for activities with Alexion, Bayer, Biogen, Chugai, Celgene, IQVIA, Merck, Mylan, Novartis, Sanofi Genzyme, Roche; as well as research support from Chugai and Diamed.

IA received received compensation for activities with Roche, Alexion, Santhera as well as research support from Diamed.

JH reports a grant for OCT research from the Friedrich-Baur-Stiftung and Merck, personal fees and non-financial support from Merck, Alexion, Novartis, Roche, Santhera, Biogen, Heidelberg Engineering, Sanofi Genzyme and non-financial support of the Guthy-Jackson Charitable Foundation, all outside the submitted work. JH is (partially) funded by the German Federal Ministry of Education and Research (Grant Numbers 01ZZ1603[A-D] and 01ZZ1804[A-H] (DIFUTURE)).

CL received a research grant by the German Federal Ministry for Education and Research, BMBF, German Competence Network Multiple Sclerosis (KKNMS), grant no.01GI1601I, received consulting and speaker's honoraria from Biogen Idec, Bayer Schering, Daiichi Sanykyo, Merck, Novartis, Sanofi, Genzyme and TEVA.

IKP received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Adamas Pharma, Almirall, Bayer, Biogen, Celgene, Desitin, Sanofi Genzyme, Merck, Novartis, Roche, and Teva. She received research support from the German MS Society, Celgene, Novartis, Roche and Teva.

CS received compensation for activities with Bayer, Biogen, Merck, Novartis and Roche as well as research support from Novartis and MedDay.

RAL received compensation for activities with Bayer, Biogen, Celgene, Merck, Novartis, Sanofi Genzyme, and Roche; as well as research support from Biogen, Merck and Novartis.

Financial support

Development of this manuscript was supported by Merck.

Author contributions

All authors have read, commented on the manuscript and approved the final manuscript.

Acknowledgments

Medical writing and editorial support, under the direction of the authors, was provided by Markus Fischer, PhD (Fischer BioMedical Wissenschaftskommunikation, Germany) funded by Merck, according to Good Publication Practice guidelines. The authors were responsible for all content and editorial decisions, and received no honoraria related to the development of this publication.

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