

The need for a strategic therapeutic approach: multiple sclerosis in check

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Abstract: Multiple sclerosis (MS) is the most common chronic autoimmune neurological disease. Its therapeutic management has drastically evolved in the recent years with the development of specific disease-modifying therapies (DMTs). Together with the established injectables, oral and intravenous alternatives are now available for MS patients with significant benefits to modulate the disease course. Certain drugs present with a higher efficacy than the others, profiles and frequencies of adverse events differentiate as well. Thus due to the several and different treatment alternatives, the therapeutic approach adopted by neurologists requires a tactical focus for a targeted, timed, and meaningful treatment decision. An integration of rational and emotional control with proper communication skills is necessary for shared decision-making with patients. In this perspective paper, we reinforce the necessary concept of strategic MS treatment approach using all available therapies based on scientific evidence and current experience. We apply a didactic analogy to the strategic game chess. The opening with oriented attack (i.e. already in early disease stages as clinical isolated syndrome), a correct choice of chess pieces to move (i.e. among the several DMTs), a re-assessment reaction to different scenarios (e.g. sustained disease activity, adverse events, and family planning) and the advantage of real-world data are discussed to try the best approach to ultimately successfully approach the best personalized MS treatment.

Keywords: disease-modifying therapies, DMTs, multiple sclerosis, strategy, treatment, chess

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Introduction

Multiple sclerosis (MS) represents the most frequent chronic autoimmune disease of the central nervous system (CNS).¹ Of particular concern is the fact that the first diagnosis is established predominantly in young adults at the peak of their productive age with a pronounced female–male proportion.² Approximately 85% of patients present initially a relapsing remitting multiple sclerosis (RRMS) with recovery of neurological symptoms after relapses. Among these patients, it is estimated that a variable proportion (up to 80%) will develop secondary progression of neurological disability, mostly independent of relapses, in the secondary progressive multiple sclerosis (SPMS). Around 15% of the patients present no clear relapses in the disease course, showing a progressive disability progression since the beginning of the disease, where a

primary progressive multiple sclerosis (PPMS) is diagnosed.^{1,3}

MS is a multidimensional heterogeneous disease, in which clinical manifestations are extremely variable in all MS subtypes as inflammatory or demyelinating lesions can affect every localization of the CNS. MS is also a chronic disease, where no cure or definitive treatment has been approved so far, although novel therapies in the disease management have emerged in the recent years. Since the first approval of interferon beta-1b in 1993, dramatic advances have been made regarding the pathophysiology, diagnosis, and treatment of MS.^{4,5} Newer disease-modifying therapies (DMTs) present high efficacy in the prevention of further disease activity or clinical progression through modulation of the immune system or even targeted depletion of certain

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immune components.⁶ DMTs may result although in adverse reactions or events that may be determinant to the therapeutic adherence as they could significantly alter the quality of life of MS patients.

However, as MS is a multidimensional variable disease with uncertain and unpredictable disease course and phenotypes, the risk–benefit assessment of each DMT may vary between patients and at different timepoints of their disease. The different expectations of physicians and patients, prognostic factors, and adherence are also extremely variable among people with MS and thus, a strategic approach for treatment decisions is fundamental in the management of this disease.⁷ Controlled clinical trials have been an important and classical source of data for the currently care of patients. Nevertheless, clinical trials with the statistical approach using the rule of large numbers resulting in statistically meaningful conclusions are not able to solve all individual treatment questions as they are not powered to draw individual treatment decisions. In addition, advances in data science and newer sources of clinical evidence are currently revolutionizing knowledge in MS. Multidimensional data from real-world settings could offer a more robust and practical source of information with great value for neurologists.⁸

MS therapy is evolving from unspecific agents with unclear pharmacodynamics toward molecular-specific treatments. Currently, the European Medicines Agency (EMA) has already approved 17 DMTs for the treatment of this disease. Different efficacy profiles have been described for several subcutaneously, intramuscularly, intravenously, and orally applied drugs. Their mechanisms of action, adverse effects and safety profiles, as well as the clinical experience with each of them, vary drastically between drugs and their specific application in the course of the disease is still not completely standardized and understood. For the PPMS and SPMS, first therapeutic options were approved only in recent years.

Considering the current available treatment options, neurologists need a strategic approach for rational therapeutic decisions and individual disease management. In current times with more and better options, complex strategies may be necessary to take advantage of the available resources. Using analogies with one of the most

popular board games in history (chess), we reinforce in this review the focus on the long-term strategic approach for the treatment of MS patients, beginning on the first suspect of the disease with radiologically or clinically isolated syndrome, through the first diagnosis and up to further disease scenarios such as increased disease activity or therapeutic adverse events. We review the current evidence and standards for the treatment choice to discuss further tactics to adopt in future movements. We base our considerations in the view of current MS practice according to European and local guidelines.

Characteristics of a good (chess) neurologist

Good neurologists tend to be extremely investigational and analytical, with curiosity for a proper understanding of the patient's disease in order to make an appropriate diagnosis and treatment plan. They should be patient, organized, and focused individuals, as neurological diseases require frequently a detailed examination and analysis of several paraclinical outcomes. In addition, a high degree of sociability is ideal for an emphatic relationship with the patients but also with a required flexibility to address their need.⁹ These characteristics are mostly shared with optimal chess players, who may overcome several scenarios in a game to achieve their objectives. A development of social, clinical, and scientific skills is fundamental for an excellent MS specialist and for a further therapeutic approach of the MS patient.

Choose the MS strategy (and aim for the king)

Before participating in important tournaments, chess players usually improve their game by learning established strategies and tactics. MS specialists should also understand the different assets and approaches very well, which are currently available for the treatment of the disease. This implies not only simply the DMTs and their effectivity, but also detailed data regarding the diagnosis, timing, course, and evolution of the disease. Understanding this frame and deep knowledge is prerequisite to follow a strategic approach in MS management.

An optimal treatment goal would be the stabilization or slowing of the disease activity and progression. Nevertheless, just as not every chess game can be won, not every disease challenge will accomplish this objective. Nevertheless, it should

be considered that even if disease activity and disability development could not be stopped, an improvement of the quality of life can still be obtained by symptomatic treatment (including e.g. physio-, logo- or ergotherapy) or new organization of daily processes or other supportive measures. A definitive cure or complete recovery of symptoms seem to be an inadequate goal and should therefore be avoided. The recent goal of ‘no evidence of disease activity’ (NEDA, see below) appears to be a reasonable, but still ambitious status to control the disease progression especially in the long-term perspective. According to current evidence, not only clinical relapses or disease progression should be aimed at, but effects on the much more sensitive radiological or biochemical signs of inflammation and degeneration should be achieved.

It must be noted that, even though this is an ambitious and ideal goal, the strategy must be adapted to the changing situations along this unpredictable disease. Tactics in chess and in MS involve the selection of movements and the calculation of their consequences on the short term. Together with the long-term strategy, a tactical monitoring and reaction with different DMTs or symptomatic treatments is needed to overcome (still) unpredictable changes in the disease course. MS specialists and chess players cannot calculate and predict the evolution of every patient or game they are involved and therapeutic goals may change along the management of the disease. In chess, certain situations require a defensive approach to avoid a defeat (aiming for a tie), instead of a checkmate. Risk factors, clinical trials, or other data source may allow to generate a prognostic estimation for a patient, but MS is still an extremely unpredictable disease.

The use of demographic and clinical factors, which may be associated with a more aggressive clinical course (e.g. age > 40 years, male sex, comorbidity, relapse frequency or recovery, magnetic resonance imaging (MRI) phenotype) should be individually considered in patients.^{10,11} Hopefully, further developments in data science could help a closer prognostic of the course of each patient and even simulate outcomes with several DMTs (e.g. through the use of digital twins).¹²

The final decision-taking should always be performed in consensus with the patient and

considering, together with the profile of each DMT and the therapeutic goals, the personal preferences of the patients after a detailed explanation of the diagnosis and indication of the immune therapy.¹³

Tactical ‘Opening’ of MS treatment: your first moves are important!

Neurologists and patients begin the match against MS already after a first clinical event or even first radiological signs of relevant CNS inflammation are evidenced. In chess, the first movements have a special importance as they set the field for the whole game. These ‘openings’ may condition the whole strategy and should be performed with caution. A good ‘therapeutic opening’ may also help control the setting of the disease, where a proper discussion of the diagnosis and treatment alternatives is performed and the future relationship with the patient is founded.¹⁴

The first moves of the game against MS are completed already when patients have a clinically isolated syndrome (CIS) or even a radiologically isolated syndrome (RIS). CIS is defined as a first clinical inflammatory episode without the formal fulfillment of the MS diagnosis criteria.¹⁵ This manifests typically as an optic neuritis, transverse myelitis, or brainstem syndromes, although a wide spectrum of clinical presentations is possible.¹⁶ Although patients frequently have a complete recovery after this first clinical manifestation, the process of neurodegeneration begins already at this stage of the disease supporting early therapeutic actions.¹⁷ Patient with imaging findings suggestive of MS without clinical symptoms are, on the other hand, diagnosed as RIS.

A good opening with DMT has already demonstrated to have positive long-term consequences as there is enough clinical evidence of a benefit of these drugs already in this phase of the disease:^{18–23} In patients with CIS, the probability of a new MS diagnosis had a decrease of up to 35%–50% after 2 years and 44% after 3 years through use of different interferons and up to 45% in the PreCISE study comparing Glatiramer acetate with placebo. Patients early on in treatment with these DMTs also reflected a decreased detection of newer or enlarging MRI lesions. In Europe, different interferons and glatiramer acetate are available for this indication. Therefore, the use of DMTs should be recommended already early in this case.

In the case of the therapeutic approach of patients with RIS, the decision of an early begin is more controversial. Data supporting the clearly indication of DMTs in these patients is currently lacking, although several trials are under development (including among other teriflunomide, dimethyl fumarate, or even bacille Calmette-Guérin).²⁴ Practitioners tend to be more conservative with a continuous monitoring and clinical and radiological follow-ups, as a consensus in 2014 in the United States reflected.²⁵ There has been although a statistically non-significant increase in the proportion of neurologists from that population, who would initiate treatment from 10% to 26% between 2011 and 2014. A distinction was made according to the characteristics of the MRI lesions: in the case of more than two active lesions (reflected through gadolinium enhancement), a consensus was established to initiate treatment. Together with the MS patient, the indication of an off-label therapy should be discussed in these cases.²⁴ The 2018ECTRIMS/EAN MS treatment guidelines did not approach this specific point.²⁶

After the initial event, patients will present further inflammatory events. Currently, the most-used diagnostic criteria for this purpose are the 2017 revisions of the McDonald criteria.¹⁵ The fundamental includes dissemination in space and time. For the dissemination in space, MS-suspicious lesions in at least two anatomical locations of the CNS are required. It is worth mentioning that the optic nerve enhancement does not count in these criteria. The appearance of newer lesions over time or the simultaneous detection of lesions with and without gadolinium enhancement serve for the fulfillment of dissemination in time. In the latest revisions, oligoclonal bands specifically in the CNS can be used as a complement of the dissemination in time criteria.

The latest revisions of the McDonald criteria allow an earlier and sensitive diagnosis still with a high specificity. Many patients, who with older definitions were defined still as having a CIS are now categorized as RRMS (e.g. when positive oligoclonal bands are present). A MS diagnosis certainty has an enormous impact in the management of the disease as not only more DMTs are available for RRMS than for CIS (including oral drugs, which may be attractive for the patients), but also the certainty of having a clear diagnosis increases

the therapeutic adherence and makes easier a further planning of the strategic approach. However, these criteria should be applied with caution in suspected cases and when differential diagnosis are overruled as this may also have an important therapeutic relevance (e.g. certain MS therapies may be harmful in other diagnosis such as neuro-myelitis optica spectrum disorders).

The discussion of the rationale of frequent monitoring including neurological and imaging controls is necessary at the first diagnosis of CIS or MS as well. Patients should be aware of the possible course of the disease and the characteristics of MS-related symptoms, relapses, and complications. A frequent MRI monitoring is widely recommended to detect subclinical disease activity but should be adapted to the therapy goals and reality of each patient, especially if this may have a therapeutic consequence. Consensus recommendations have addressed this point where patients, including RIS, should be offered an MRI follow-up frequently within 6–12 months to detect dissemination in time or in space.^{25,27} Primarily, this should be performed through brain MRI as the value of successive spinal cord in still not established.²⁷ In early disease stages, a goal of yearly MS-focused MRIs is to be strived for an early potential diagnosis and eventually DMT change. The exact frequency and eventually the use of spinal cord imaging should be individually considered. A consequent and responsible use of diagnostic resources is crucial for an adaptive monitoring. This multidimensional monitoring and assessment of the actual state respective phenotype is crucial for the next diagnostic and therapeutic steps (Figure 1). An emergency consultation should be available for the patients in the case suspect of a new relapse or relevant clinical progression for treatment for a prompt evaluation and confirmation the event.

The acute treatment of relapses should depend on their severity and functional disability aiming a prompt recovery and ease of acute disease burden. However, treatment of acute relapses may have no significant impact on future disability progression and patients should be informed of this to avoid unrealistic goals or abuse of treatment.²⁸ Classically, corticosteroids at high doses have been used as a common practice standard.²⁹ This can be performed in outpatient clinics or in stationary settings depending on the symptoms and severity of the event. A re-evaluation should be performed

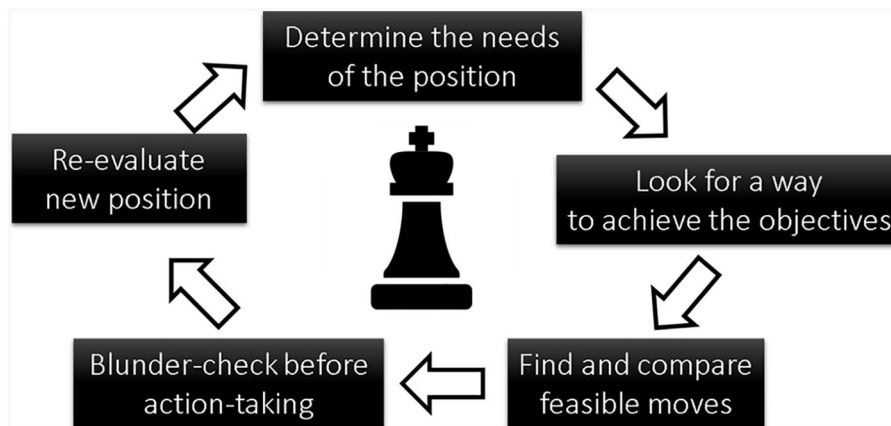


Figure 1. Evaluation of chess moves. Approach for decision of moves in chess, which can also be partially adapted in MS management (see text).

approximately 14 days after this pulse therapy to assess if a further administration is necessary. Alternatively, an oral administration of equivalent doses can be offered in certain situations (e.g. by logistic impossibility for the patient or COVID-19 pandemic). Although this may have a similar efficacy compared to the intravenous administration, due to the uncomfortable posology (up to 50 tablets prednisolone per day), a compliance may not be optimal. In severe cases, by contraindications against corticosteroids or in case of insufficient improvement, plasmapheresis can be considered.²⁹

Timed chess

Playing timed chess, players have only limited time left on the clock to consider every possible scenario. Not every of these movements may lead to a checkmate; an inexperienced player may waste precious time analyzing futile plays. Great masters can recognize at a first look which is a winning move and take a quick decision to save time, which may be necessary in future stages.

In MS, the widely used concept of the ‘time is brain’ therapeutic challenge also applies. The timing of the initiation of immune therapies may be a key factor in the future prognosis and disease development. Brain and cognitive reserves may be saved or spared if a pertinent move is performed when necessary. The timing of the first MS diagnosis and treatment has been widely addressed by Giovannoni *et al.*³⁰ as part of an international consensus (Brain health: time matters in MS), where several factors that may influence an early

approach were discussed. Among others, patient awareness about neurological complaints, early referral to neurologists (and if possible to MS neurologists) for a prompt diagnosis, management in setting of specialized clinics and the use of high-quality diagnostic resources appear to be fundamental for an early treatment.³⁰

Furthermore, currently expected, achievable, and aspirational goals for a prompt disease management have also been proposed as result of an international expert consensus.³¹ Clear recommendations addressing the referral to diagnosis after first clinical manifestations, formal MS diagnosis, discussion of treatment options and disease course, routine monitoring of management of acute symptoms were included. This initiative offers a clear timed goal for early interventions and relevant modification of the disease course. In example, an MRI and an MS diagnosis should be performed 4 weeks after a referral to a neurologist in order to offer appropriate DMTs. In an ideal setting, patient could begin with a DMT as soon as after 3 weeks after the diagnosis.³¹

As commented above, the first diagnosis of a demyelinating event, already at the time of CIS, is a key time point for a modification of the patient’s outcome. The time for the first MS diagnosis can be delayed in several patients through immune therapy with interferon or glatiramer acetate.^{20–23} In addition, a better long-term outcome is described in patients treated early with DMTs.^{32–36} After a first MS diagnosis, the clinical scenario

may be slightly different as a certain diagnosis could alter the disease approach and therapy decision by the patients, and other DMTs may be available. This represents not only in relapsing patients but also in active progressive MS a window of opportunity for a positive alteration of the disease course. MS damage is to date irreversible and the early intervention through DMT may support the compensatory mechanisms occurring in the CNS.

Besides a decreased clinical disease activity with fewer relapses or inflammatory MRI lesions, early treatment with current MS drugs could delay the diagnosis of a secondary progressive course. An analysis of a Swedish analysis suggested a treatment effect on the time for the SPMS diagnosis (hazard ratio (HR) 0.32 for men and 0.53 for women).³⁷ A cohort study in Italy showed that patients with more recent MS diagnosis had a longer time to achieve an EDSS score of 6.0, possibly due to the more standardized use of DMTs in the current century compared to those who had a diagnosis in the 90s.³⁸ Similarly, patients seem to develop a secondary progression at a lower rate in the current era, with only 18.1% after almost 17 years median follow-up.³⁹ Timing appears to be an important factor, as patients with initiation of DMTs in the first 5 years of disease onset had a 33% lower risk of conversion to SPMS than those who started it afterwards.⁴⁰ However, a systematic review could not confirm long-term benefits of DMTs, although they were present in short term due to methodological inconsistency.⁴²

For a more efficient use of time in MS, the right DMTs should be tactically chosen to affront the disease. Although DMTs can be stopped or adjusted in the case of continuing disease activity, once a movement is made, time cannot be recovered and decisions cannot be changed afterwards. Frequently, it is more appropriate to select a 'strong' piece instead of soft attempt for disease stabilization with first-line drugs (see below).

Thus, these early disease stages are also critical for the optimization of the DMTs as recurrent relapses or newer MS lesions in follow-up MRI evaluations in the first year of therapy may predict an increased risk of therapy failure.⁴³ To achieve a better outcome, an active inflammatory state should be recognized and the immune therapy adjusted as possible.

Attack and react

Similar as in chess, every piece may play a different role to achieve a final common goal. In the MS treatment, every DMT has currently their indication and individual characteristics to be considered. A re-thinking of the treatment algorithms is necessary to optimize the possible benefit of newer DMTs. Classically, the sequencing of DMTs focused on an 'escalation approach', where patients are successively treated with therapies from a 'basic' or first-line spectrum and re-adjusted to more effective alternatives depending on the disease activity over time.⁴⁴ With the development of newer and more targeted MS specific DMTs, an induction approach has emerged as an alternative possibility, where high-efficacy DMTs are used to obtain a remission of active diseases.⁴⁵ It is important to prepare, when possible, a second option or exit strategy scenario how the treatment plan B could look like. In both scenarios, a baseline MRI is recommended before starting or switching the DMTs for further monitoring, with a further new baseline at 3–6 months to detect lesions that appeared before therapeutic onset.²⁷

Safety profiles and wide experience with first-line DMTs support using them in mild forms of MS. However, an induction or 'hit hard and early' strategy seems to be an appropriate approach in those with highly active forms of the disease, where the clinical benefit toward a remission of the disease activity may overweight possible risk for adverse effects. A cohort study with 592 patients could demonstrate a better disability status through lower EDSS scores in patients who received early high-efficacy DMTs compared to those who were treated with first-line therapies at early disease phases.⁴⁶ This approach, also known as 'hit hard and hit early' is also supported by a large study including 1555, where patients who received initially fingolimod, natalizumab, or alemtuzumab were associated with a 44% lower risk of conversion to SPMS compared to those who were treated with interferon beta or glatiramer acetate after 5.8 years median follow-up. These had also a lower risk of secondary progression than the untreated group of patients.⁴⁰

The economic impact of MS drugs and of the disease itself is an important factor that should also be considered.⁴¹ Although a single dose of newer DMTs seem to be more expensive than the well-known immune modulators, studies have shown a positive cost-effectiveness in real

world of the use of, for example, natalizumab or fingolimod compared to first-line drugs.^{47,48} In addition, the prevention of secondary health-related costs as part of an SPMS course, which may be delayed through DMT should also be considered in this decision.⁴⁹ Thus, an early escalation may be more cost-effective than switching between therapeutics with lower effectiveness.

Considering that the high-efficacy DMTs have been only recently developed and the complete safety profile (especially regarding long-term effects) is unclear, the decision of an early aggressive treatment should be taken together with the patients (and eventually with his or her family members). Currently, further studies are ongoing to further determine the benefit of this strategy, which may support the clinical decisions, such as the TRaditional versus Early Aggressive Therapy for MS (TREAT-MS) or the Determining the Effectiveness of earLy Intensive Versus Escalation Approaches for the Treatment of Relapsing-Remitting Multiple Sclerosis (DELIVER-MS) open trial.^{50,51}

The definition of highly active MS may also be difficult as there is currently no defined consensus for mild and highly active MS according to the EMA (Figure 2). This agency recommends a clear definition in of this form in the study protocols. This is currently based on clinical and imaging aspects, such as relapses (including frequency, severity, and recovery), gadolinium-enhanced lesions, or disability accumulation. A *post hoc* analysis of the alemtuzumab CARE-MS I and II trials used in example four definitions, using a primary definition (two or more relapses in the previous year and one or more gadolinium-enhancing lesions in an MRI) and other definitions with focus on relapses, MRI, or previous treatments.⁵²

A focus of future research should include the recognition of disease patterns in early disease stages using newer diagnostic resources, which may not only support the categorization of highly active MS, but also individualize the therapy decision as certain disease phenotypes may respond better to certain DMTs. The recognition of the 'game characteristics' is important for MS specialist as it is for a chess master. As example, a prospective study could determine that patients with ≥ 2 Gd-enhancing lesions or spinal cord lesions at baseline had a three to almost five times higher

risk of secondary disability accumulation after 15 years.⁵³ These patients may be good candidates for a more aggressive therapy strategy.

Another promising piece in the treatment of MS is the use of stem cell therapy through autologous bone marrow transplantation. Through several mechanisms, which are still not completely understood, a reset of the immune system, repair, and remyelination or a modulatory effect on MS patients through hematopoietic or neural cells in example.⁵⁴ Specially young patients with highly active disease phenotypes may benefit from this novel therapy.⁵⁵ However, even though advances in safety profiles of stem cell therapy in the recent years, there is still lacking evidence for a standard implementation in clinical care. Possible, bone marrow transplantation may emerge as a game changer in the coming years of MS management.

Check the strategy continuously and recognize the opponents' movements

As commented above, a close monitoring is required as part of the assessment of patients to promptly detect disease activity. In chess, not only the own movements are important, the analysis of the opponent is crucial to react at a right time and have a favorable scenario on time. For patients and physicians, the opponent is the disease itself, which should be observed and characterized carefully and continuously.

The selected treatment concept should be re-assessed in confirmed active MS patients with first-line therapies, even (and specially) in early disease phases. Here, the disease monitoring through evaluation of clinical and subclinical activity may reveal a change in the disease situation and require an adaptation of the treatment concept. MS disease progression can be multifactorial and be reflected in several ways (Figure 3). Evaluation for relapses, frequent imaging through regular MRI or use of newer blood biomarkers as, for example, serum neurofilament plays an important role in this aspect of the disease management. The use of standardized and reliable clinical outcome measures is important for the reliability of the follow-up. In MS, no standard is established to define disease activity or progression.⁵⁶ However, tools for the assessment of the strategy should be carefully selected according to the resources in the clinical setting. In case of detected

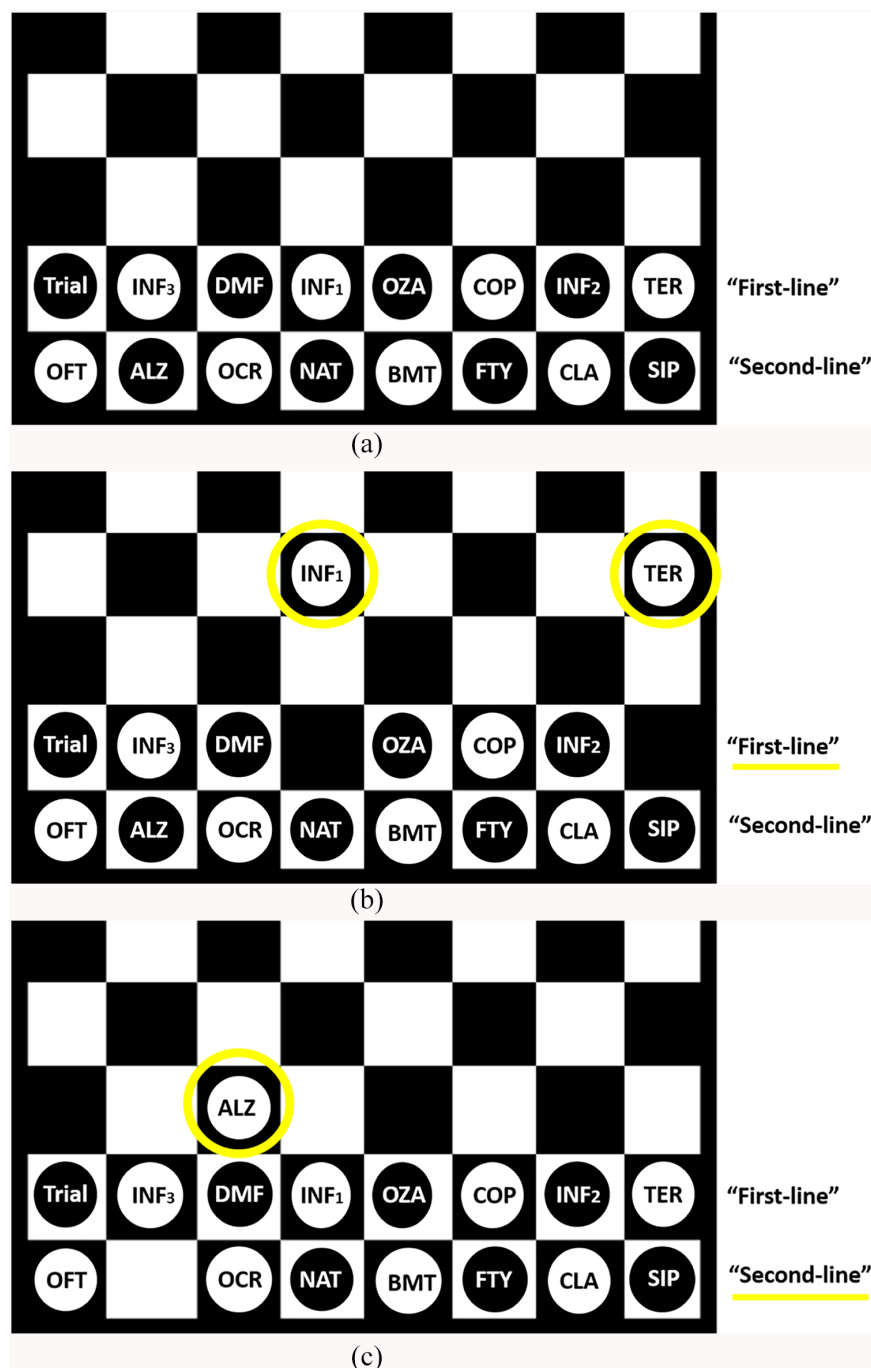


Figure 2. Example of a chess-based therapy strategic approach of multiple sclerosis therapeutics: (a) the initial setting for the game is presented with first- and second-line disease-modifying therapeutics (DMTs) with different characteristics and place on board. The board and available DMTs as well as their position at the first approach may vary between patients due to several factors (e.g. personal preference, comorbidity, and adverse reactions). Depending on this, the initial move should be determined and further steps planned already at this point of the patient care. (b and c) reflect the escalation and induction approach respectively. Several drugs have been approved in both settings, some of them with similar mechanism of action but different posology (e.g. interferon administrations). In certain cases, a different 'second-line' DMT may be used as initial therapy depending on the disease phenotype. Certain patients may benefit at any disease phase of inclusion in clinical trials, where newer DMTs are being developed.
 ALZ, alemtuzumab; BMT, bone marrow transplantation; COP, glatiramer acetate; DMF, dimethyl fumarate; FTY, fingolimod; INF1-3, interferon at different preparations; CLA, cladribine; NAT, natalizumab; OFT, ofatumumab; OCR, ocrelizumab; OZA, ozanimod; SIP, siponimod; TER, teriflunomid.

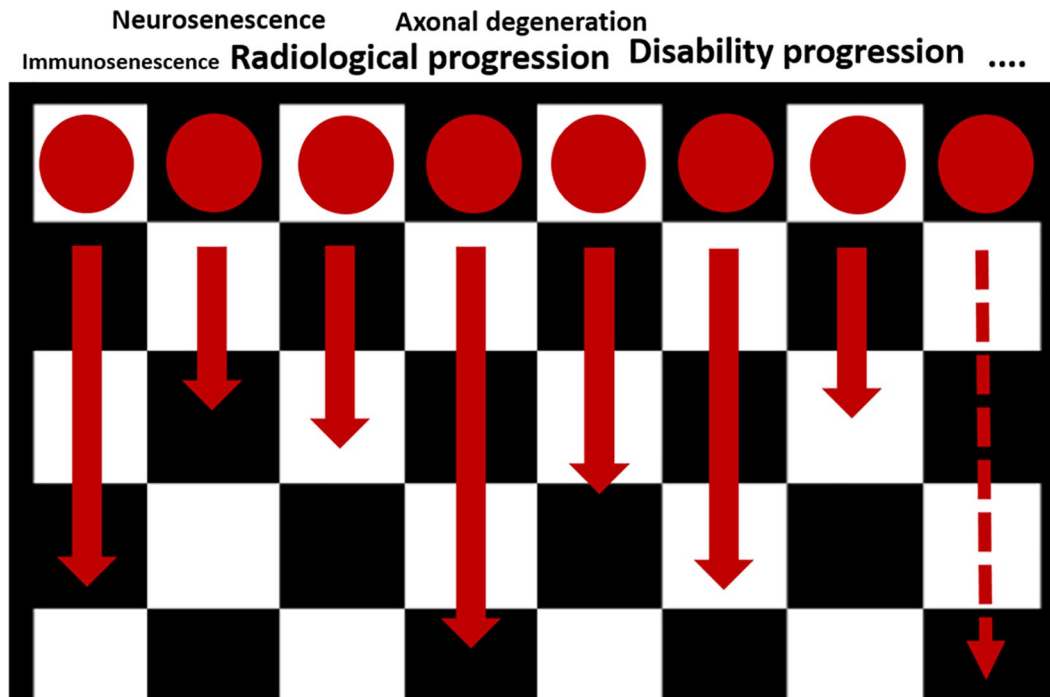


Figure 3. Didactic presentation of selected assets of MS as an opponent to be considered in the management of the disease. Clinical and subclinical factors may contribute to the disease progression and eventually switch to a secondary progressive disease phenotype. Some of these may inevitably occur age-related (such as immunosenescence or neurosenescence) and appear at different rate.

clinical or subclinical disease activity, a switch to a more effective DMT or a newer course of an induction therapy should be considered.

Adverse events, not infrequent severe, are also frequent reasons to discontinuation or switching of DMTs.^{57,58} Local or systemic reactions after use of injectable DMTs, such as interferon presentations or glatiramer acetate, are already frequent causes of switch of these DMTs, particularly in early treatment.⁵⁹ Elevation of liver enzymes or persisting reduced lymphocyte counts may lead to a discontinuation of other DMTs such as teriflunomide or dimethyl fumarate. More severe complications are also described with newer DMTs. A well-described complication is the progressive multifocal leucoencephalopathy (PML), an opportunistic infection that may occur under treatment with natalizumab and that is clearly described in the product information.⁶⁰ Certain DMTs require a specific screening procedure or a safety pause interval between drugs before application. Also in the case of therapy with natalizumab and the risk of PML, the screening of anti-JC-Virus antibodies before and during treatment course as well as

regular monitoring (especially beyond 2 years of treatment duration).

An interesting and ambitious goal with the MS therapy is the achievement of a state of ‘no evidence of disease activity’ (NEDA). This composite outcome integrates clinical and imaging evaluations for the therapy monitoring and disease control.⁵⁶ This approach requires regular clinical evaluations and MRI evaluations. As endpoint, a state free of clinical relapses, confirmed EDSS progression, new or enlarging T2 lesions as well as Gd-enhancing lesions on MRI are on focus.⁶¹ A great support for clinical practice could be the use of a multifactorial model as proposed by Stangel and colleagues, where different domains additional to the used as part of NEDA are used to evaluate disease activity creating a traffic-light-similar score (MSDM score).⁶² Neurophysiological variables as well as the clinical relevance in daily function should be assessed, and scores are also currently under development to support the detection of SPMS (e.g. the MS progression discussion tool).^{63,64} The recommendations of a Canadian work group have also

addressed this point discussing the described lack of consensus on definition of an adequate treatment response.¹⁰ This group presented minor and major criteria for a therapy switch according to relapse rate, severity, recovery, as well as MRI criteria. Nevertheless, the use of NEDA or other strict strategies should be accompanied by clinical reasoning and communication with the patients avoiding a total dependence of such an endpoint for the MS management. The long-term prognostic value of NEDA goals is under critical discussion. A prospective with data from 517 MS patients reflected that neither clinical nor radiographic features after 2 years of follow-up had prognostic value after 10 years.³⁹ The possible influence of active spinal cord lesions not captured with brain MRI, progressive degeneration, or transient remission at assessment was discussed. Another study showed the difficulty of maintaining a NEDA status after 7 years, where an NEDA after 2 years follow-up could serve as a prognostic marker of no or lower future disability to this point.⁶⁵ Even though NEDA may seem an ambitious endpoint, it could be a desirable goal for MS patients. Its long-term prognostic value remains unclear, but it could serve as an orientation for further clinical decisions. Discussions of this and other goals with the patient to establish a personalized objective (as commented above) is necessary in this strategic setting. An alternative goal of 'minimal evidence of disease activity' (MEDA) has been mentioned in the previous Canadian recommendations,¹⁰ which may be more practicable in clinical settings.

As part of the monitoring, the pathophysiology behind the neuroinflammation in CNS should be considered in the imaging control evaluations. Not only a complex inflammation plays an important role, resulting in clinical relapses and newer or Gd-enhancing lesions, but also a progressive axonal degeneration, which can be partially evaluated with atrophy measures.³⁶

In case of disease activity, neurologists and patients may have a situation with three alternatives: maintaining current therapy with further follow-ups, switching to another DMT with a similar efficacy profile or switching to a DMT alternative with a higher efficacy profile. Regardless of the preferred approach by the neurologist, decisions should be made, as commented above, always together with the patient in a shared decision-making process.

Decisions should avoid a compulsion to move (in chess known as *Zugzwang*), when players, usually at an adverse endgame situation are forced to make an undesirable move. Treating neurologists should address carefully off-label therapies or decisions without medical evidence as they may be no benefit for the patients.

Evolution of data science and use of big data, also obtained from real-world settings, will probably represent a game changer tool for the decision of further moves and understanding of the disease.⁶⁶ Chess players can study their future opponents through data banks and records of previous matches to elaborate a strategy and recognize how they react in different situations. This is increasingly possible in MS as real-world data are used to understand the disease.

Coping with emotions during the disease approach

In MS, a rational, evidence-based approach accompanied with firm emotional control in the decision taking is strongly required. MS specialists will face different patient profiles, ranging from young women at the beginning of their life with almost no disability to more dependent older patients in more advanced stages of the disease. Social skills are extremely necessary to manage every possible scenario. A realistic treatment goal should be discussed with honesty and clear communication skills in early phases of the disease as soon as the MS diagnosis is suspected.⁶⁷ A consideration of the unclear and so far not completely understood disease courses and the varying phenotypes is a basis of further planning. The MS phenotype and the use of DMT may affect the expectations and satisfaction of MS patients and should be considered at the therapy planning.⁶⁷

Relapsing and progressive MS patients present with different disability profiles, different requirements in their treatment and monitoring. While RRMS frequently reflect a complete recovery of neurological symptoms after relapses, SPMS and PPMS patients reflect a progressive disability progression, which may be difficult to be detected by physicians and even patients themselves.⁶⁸ Not uncommon in clinical practice is a questioning from RRMS patients regarding the necessity of a DMT in early disease stages and even reject an immunomodulatory therapy if they do not perceive chronic MS symptoms. A communication

of the subclinical inflammatory process and the potential transition into a progressive course, which may be delayed with an early prophylactic therapy, should be properly discussed.⁶⁹

Frequently, progressive patients and those with an incomplete remission after relapses may expect a complete recovery from neurological deficits and return to normal physical capacities. Even though physiotherapy and lifestyle changes bring an improvement in the quality of life,⁷⁰ physicians should discuss, with the necessary empathy, these situations and respective goals with their patients. To date, no remyelination therapy has successfully overcome clinical trials in order to be approved although promising animal studies have been published.⁷¹ In individual cases, an improvement of baseline symptoms can be seen after certain DMTs, although this may not represent the common rule.

Endgame?

Chess games are divided frequently in three phases: opening, midgame, and endgame. Although the first two phases can be closely related to MS strategic management, they may substantially differ in the latter. MS is a chronic disease, and no cure or definitive treatment has been identified to date. Neurologists accompany patients lifelong through their disease burden. There is still not enough data to support a limited treatment time with the available DMTs. Therapies are generally stopped due to intolerance or risk of severe adverse events. As patients age, a process of immunosenescence occurs with alterations in the regulatory mechanisms of the immune system.⁷² MS coexists in geriatric patients with several diseases, not only neurological but also cardiovascular or musculoskeletal, which may affect the quality of life. SPMS overlaps with these other factors requiring a different and rather supportive treatment approach. A clear strategy including the duration of immune therapies, tolerance of adverse effects or benefit of interventions in this group of patients would be important, but it is still not yet available due to missing data.

This MS–chess analogy reflects several similarities in both strategic approaches. In the lifelong challenge to fight against MS, neurologists share personal characteristics, mentality, and actions with grand chess masters. However, the therapeutic

approach of MS patients is of course more complex than this popular game. Continuous medical education with update of current scientific information and clinical experience is fundamental to elaborate tactics and strategies for the benefit of the patients. That is why we have established a master course “Multiple Sclerosis Management” in Dresden.⁷³ Especially nowadays, as DMTs are rapidly evolving, MS specialists should offer at the proper moment the best available treatment for each patient. Data from real world is illustrating the benefits of early medical treatment and may provide supporting hints in the future strategies. A tendency of MS specialization and treatment in MS centers may facilitate the theoretical and practical formation for a better management of the disease. Both MS and chess require study and playing, theory and practice, in order to become a great MS chess master and dominate the game against this challenging heterogeneous disease. Digital technology may assist to optimize individual MS treatment as in chess, the computerized chess player has improved significantly in the past years.⁷⁴

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Supplemental material

Supplemental material for this article is available online.

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