Should MS be Treated by Escalation or Induction Therapy?

Ines Lazibat[1], Branimir Nevajda[1], Gordan Grahovac[1] and Vesna V. Brinar[2]

[1] University of Zagreb, University Hospital Dubrava, Department of Neurology, Zagreb, Croatia
[2] University of Zagreb, School of Medicine, Zagreb, Croatia

A B S T R A C T

MS is a chronic, increasingly disabling disease whose long-term outcomes determine the key social, medical and economic impact of this disease. Disease-modifying therapies (DMTs) for multiple sclerosis (MS) are prescribed to delay disease progression and to protect a patient's functional capability. The concepts of escalation and induction immunotherapy in MS represent different therapeutic strategies for the treatment of MS. Both strategies may be valuable options for patients starting on DMT, however, induction therapy mainly focuses on patients with very aggressive course of MS from the onset. Using a patient unique approach to selection of treatment, MS can be effectively control disease and may delay or even prevent the development of secondary progressive MS.

***Key words**: Disease-modifying therapy, multiple sclerosis, escalation therapy, induction therapy*

Introduction

When a patient is experiencing the initial symptoms of multiple sclerosis (MS), he or she is at a mean age of 30 years and will usually live for another 3 to 4 decades[1]. Long-therm outcomes determine the key social, medical and economic impact of this disease. Disease-modifying treatments (DMTs) are prescribed to delay disease progression and to protect a patient's functional capability. The paradigm of pathogenesis of multiple sclerosis (MS) is still a topic of discussion and debate among controversial positions. The currently established stance in which MS is an autoimmune process led by an inflammatory demyelinisation disease counters the theory that MS is actually a neurodegenerative disease, either primary or associated with age[2]. Research has shown that there is support for both scenarios and that a »demyelinisation syndrome« implies various types of damage, which suggests a range of mechanisms involved in their development. In addition to focal demyelinisation, MS is characteristic due to the diffuse appearance of damage to normal-appearing white matter (NAWM), axonal damage that can be of varying intensity, and brain atrophy[3,4]. The acute phase of the disease is marked by focal demyelinisation with post-contrast imbibitions, while the progressive phase of the disease is dominated by atrophy of the brain and loss of axons, which is correlated to the degree of neurological disability. The relapsing-remitting form of multiple sclerosis is classically considered a biphasal disease with relapses of a potentially reversible phase of the disease, correlated with inflammatory demyelinisation and a secondary potentially irreversible phase of the disease that is marked by critical axon loss. The inflammatory changes are less pronounced in the later phases, though the disease shows increasing progression. This dissociation between the intensity of inflammation and the progressive development of neurological disability represents the inflammatory-neurodegenerative paradox that is characteristic of MS, and which marks the transition into the irreversible phase of the disease. Numerous clinical, neuropathological and neuroimaging studies have aimed to define the mutual associations of the inflammatory and progressive phases of MS. It has long been known that early relapse impacts the long term disability in MS, though there are still uncertainties and ambiguities as to the trigger that switches relapsing-remitting MS into the secondary progressive form[5]. Some epidemiological studies of the natural course of MS have shown certain limitations regarding the influences of the inflammatory phase of the disease on the progression of disability, giving the conclusion that the relapsing and neurodegenerative phases of MS

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are mutually independent. In such a case, not only the number of relapses can have predictive value in the development of invalidity; age, sex, residual deficit after the first relapse, time to the second relapse, the total number of relapses in the first two years and the duration of the inter-relapse interval can also be valuable indicators[6–9]. Though the position on the influence of relapses on the progression of the disease is controversial, it is unquestionable that MS ultimately results in an unsustainable progressive phase with permanent invalidity of the patient[10]. The dual concept of the pathogenesis of MS significantly determines the start of treatment. In secondary progressive MS, the therapy options have been exhausted and have been reduced exclusively to the treatment of symptoms. Therefore, it is of exceptional importance to commence the treatment of MS »on time« in order to prevent, or at least delay, the undesirable final outcome of the disease. The optimal »therapy window« for MS implies the stage of the clinically isolated syndrome (CIS) and the early relapsing-remitting phase.

Treat from CIS onset – Yes or No?

The early application of immunomodulation therapy brings with it a series of challenges: from when to begin and when to possible cease therapy, which therapy strategy is optimal for the individual patient, when and how to modify the therapy in the case of an unsatisfactory therapeutic response to the basic immunotherapy? These are all challenges we face in our daily work, and these demand careful assessment based on an individual and proactive approach that is adapted to meet the needs of each individual patient (»patient unique approach«). When to begin with the application of immunomodulation therapy: in the phase of the clinically isolated syndrome, or upon the onset of clinically definitive MS? This question has been a subject of debate and there is no definitive consensus. There are two opposing positions: in the first, treatment should begin immediately after determination of a clinical syndrome suggestive of MS, while the second position can best be described by the phrase »wait and see«, which implies not introducing DMT immediately, and instead waiting and monitoring the development of events. It is difficult to say which position represents the right approach. The central questions in this context are (I) for how many of CIS patients can we anticipate a favourable natural history? (II) can these patients with a good prognosis be identified early? (III) how many disease signals are needed before a therapy should be initiated? and (IV) how do we assess the long-term benefits, risks, and burden of available therapies?[11] In daily practice, cultural differences and, in particular, economic limitations may also influence how we finally counsel a patient, since the potentially high treatment costs represent a significant economic burden for both patients and payers.[12] The criteria for the application of immunomodulation therapy after the appearance of a clinically isolated syndrome is based on assessment of the risk of CIS conversion into clinically definitive MS. Clinical studies whose results have shown that the risk of CIS conversion into clinically definitive MS is significantly less in groups of patients who received basic immunotherapy (IFN-betw and GA) in comparison with the placebo groups. This suggested that the application of immunomodulation therapy should begin already at the stage of the clinically isolated syndrome (Table 1)[13–17].

Considering that the decision to start immunotherapy has great repercussions on the continued monitoring of patients with MS, it is very important to properly select patients prior to the start of therapy, in a way that identifies patients with a high risk of conversion of CIS into clinically definitive RRMS. These are patients with severe initial symptoms and multifocal onset in the first clinical episode, especially in cases with unsatisfactory therapeutic response to pulse corticosteroid therapy, and patients without signs of clinical activity of the disease but for whom continuous monitoring of radio-morpho-

TABLE 1
CIS STUDIES WITH EVIDENCE LEVEL A

Study	Population	Treatment groups	Result
ETOMS (2001)	308 CIS and suggestive MRI	154 IFNβ-1a 22mg s.c./week 154 placebo	Conversion risk at 2 years Placebo 45% IFNβ-1a 34%
CHAMPS (2001)	383 CIS and ≥2 lesions MRI	193 IFNβ-1a 30 μg i.m./week 190 placebo	Conversion risk at 2 years Placebo 39% IFNβ-1a 21%
BENEFIT (2006)	468 CIS and ≥2 lesions MRI	292 IFNβ-1b 250 μg s.c./2 days 176 placebo	Conversion risk at 2 years Placebo 45% IFNβ-1b 28%
PRECISE (2009)	481 CIS and suggestive MRI	243 GA 20 mg s.c./day 238 placebo	Conversion risk at 2 years Placebo 43% GA 25%

CIS – clinically isolated syndrome; GA – glatiramer acetate; IFNβ – interferon-beta

TABLE 2
FIRST-LINE DRUGS AND APPROVED INDICATIONS

Drug	Dose	Route	Indications
IFNβ-1b (Betaferon)	250 mg every other day	s.c.	CIS considered et high risk developing MS RRMS SPMS with relapses
IFNβ-1a (Avonex)	30 mg 1x a week	i.m.	CIS considered et high risk developing MS RRMS
IFNβ-1a (Rebif)	22 or 44 mg 3x a week	s.c.	RRMS according to McDonald criteria SPMS with relapses
GA (Copaxone)	20 mg daily	s.c	CIS considered et high risk developing MS RRMS
Teriflunomide (Aubagio)*	14 mg daily	Oral	RRMS

CIS – clinically isolated syndrome; i.m. – intramuscular; MS – multiple sclerosis; RRMS – relapsing-remitting multiple sclerosis; s.c. – subcutaneous; SPMS – secondary progressive multiple sclerosis; *Teriflunomide (Aubagio) is approved since August 2013. Second-line drugs are natalizumab, fingolimod, mitoxantrone and alemtuzumab.

logical (MR) status regularly detects new lesions as proof of subclinical activity of the disease.

Escalating Immunotherapy

The selection of an optimal therapy strategy that can modify the course of multiple sclerosis and enable these patients to live longer lives without significant physical disability and cognitive dysfunction is a challenge in treating MS. The two strategic treatments, escalation and induction therapy, are mutually opposed[18]. The concept of escalation immunotherapy represents a treatment strategy that gives precedence to drugs with the best risk/benefit ratio, and if necessary, later sequentially advances in the treatment pyramid, introducing drugs with greater strength though usually with greater toxicity, while does not necessarily imply greater efficacy. First-line drugs in the treatment of relapsing-remittent MS are beta-interferons and glatiramer acetate (GA). These are the basic immunotherapy, such that Betaferon, Avonex and Copaxone have approved indications not only in relapsing-remitting MS but also in CIS that is at high risk for the development of definitive MS. This treatment concept represents the strategy of choice for patients with the benign form of RRMS where it is expected that the disease can be optimally controlled over a longer time period using the basic immunotherapy.

Natalizumab (Tysabri) is the first monoclonal antibody specially intended for the treatment of relapsing-remitting MS. It acts by binding on the alpha-4 integrated adhesion molecule in the endothelium of the brain's blood vessels in such a way as to block the binding of lymphocytes and their entrance into the central nervous system. The effectiveness of natalizumab was tested in two large multi-centric studies. In the AFFIRM study, the use of natalizumab as a monotherapy resulted in a significant decline in the annual relapse rate (ARR), reduced disease progression and a reduction in the number of active lesions shown on an MRI[19]. The impressive results of this AFFIRM study accelerated the approval procedure for the drug by the US Food and Drug Administration (FDA) in 2004, however, the initial approval was temporarily suspended after two cases of progressive multifocal leukoencephalopathy (PML) were reported in patients that can received a combined therapy of natalizumab and Avonex in the SENTINEL study, where the use of natalizumab was tested as an add-on therapy[20]. However, after additional careful analyses, natalizumab was re-ap-

TABLE 3
SECOND-LINE DRUGS AND APPROVED INDICATIONS

Drug	Dose	Route	Indications
Mitoxantrone (Novantrone)	12 mg/m^2 body surface area every 3 months	i.v.	Highly active RRMS or SPMS with frequent and progression of disability during first-line treatment
Natalizumab (Tysabri)	300 mg every 4 weeks	i.v.	RRMS patients who have not responded to a full and adequate course of IFNβ
Fingolimod (Gilenya)	0.5 mg daily	oral	Rapidly evolving aggressive RRMS
Alemtuzumab (Lemtrada)*	12 mg daily for 5 days at month 0, 12 mg daily for 3 days at month 12	i.v.	Rapidly evolving aggressive RRMS

*Alemtuzumab (Lemtrada) is approved since September 2013 by the EMA.

proved in 2006, though exclusively as a monotherapy line drug in patients who did not have a satisfactory response to basic immunotherapy. The most severe adverse reaction to natalizumab treatment is progressive multifocal leukoencephalopathy (PML) – a fatal, opportunistic brain infection caused by the JC virus. Its risk is estimated at 1 in 1000, and therefore patients who are potential candidates for this therapy must be carefully selected, with particular attention to previous immunomodulation or immunosuppressive therapies prior to the appropriate wash out period[21]. It is recommended that the use of immunomodulation drugs be ceased one month before, and immunosuppresants at least six months before the start of use of natalizumab.

Fingolimod (Gilenya) is the first immumomodulator that was approved by the FDA in 2010 as a first-line drug for the treatment of relapsing-remitting MS. The European Medications Agency approved fingolimod in 2011, but as a second-line drug intended for patients with active RRMS who had an unsatisfactory therapeutic response to basic immunotherapy. The efficacy of fingolimod was tested in two large multi-centric studies. The FREEDOMS study investigated the effect of fingolimod in comparison to a placebo, while the TRANSFORMS study assessed the effectiveness of varying doses of fingolimod in comparison to the i.m. drug interferon-beta 1a (Avonex)[22,23]. The results of the study proved the superiority of fingolimod in comparison to the placebo, and of the Avonex group in relation to the primary and secondary indicators of treatment outcome, which consist largely of a reduced rate of relapse at an annual level, a reduced rate of progression of disability, and significant reduction of the number of active lesions shown in the MRI.

Mitoxantrone (Novantrone) is a cytotoxic drug that induces apoptosis of the lymphocytes, and it was approved in the treatment of aggressive RRMS as a second-line drug following the results of Phase III MIMS trials[24]. This multi-centric, placebo-controlled study included 194 subjects that were treated every three months over a two-year period, and the results showed the superiority of mitoxantron in comparison with the placebo group when applied in a dose of 12 mg/m^2 body area. The efficacy of mitoxantrone was measured using combined outcome indicators, including changes in the EDSS score and mobility index after two years in comparison with initial values, the number of treated relapses, and the time to the first treated relapse. However, mitoxantrone is a cardiotoxic drug, which certainly casts a shadow on its applicability, as it requires strict supervision of the patient's cardiac status[25,26]. In that sense, during treatment with mitoxantrone, patients require permanent ultrasound and isotope controls of the functioning of the left ventricle, and if the ejection fraction is <50%, this represents a contraindication for the use of mitoxantrone. The second important risk of mitoxantrone therapy is the development of acute myeloic leukaemia, which thus requires frequent controls of the complete blood screen, not only during therapy, but also several years after the completed therapy, considering the cumulative toxic effect of mitoxantrone[27]. For this reason, the total cumulative dose may not exceed 100 mg/m^2 body area. The risk of gonadal dysfunction increases with age; in women this manifests as amenorrhea, in males as irregular spermiogram[28].

The current therapeutic algorithm for risky CIS and relapsing-remitting MS implies commencing treatment with the first-line therapy and, in the case of an unsatisfactory therapeutic response, to advance in the therapy pyramid until optimal control and stabilization of the disease is achieved. The first step in the application of this strategy may be to switch from one drug to another within the first-line. The typical approach is, for example, to replace a low dose IFN with a higher dose, or to administer it in a greater frequency, as there is B level evidence that indicates the benefits of increasing the dose and frequency of administration of IFN[29]. The second possibility in the case of an unsatisfactory clinical response or intolerance to therapy is to replace the IFN therapy with glatiramer acetete. The theoretical basis for

TABLE 4
NATALIZUMB, BENEFIT *VS*. RISK – EVALUATION

BENEFITS	RISKS
Established in clinical trials:	PML (1:1000)
AFIRM, N=942, monotherapy	
– 68% reduction in ARR	fatal opportunistic CNS infection by JSV
– 42% reduction in disability progression	subacute progressive dementia
– 92% reduction of Gd+ lesions	focal neurological deficits
	motor dysfunction
	vision loss
SENTINEL, N=1171, add-on therapy (IFNβ-1a i.m.+NZB)	Hypersensitivity reactions
Clinical experience	Opportunistic infections

PML progressive multifocal leukoencephalopathy

TABLE 5
FINGOLIMOD, BENEFIT *VS*. RISK – EVALUATION

BENEFITS	RISKS
Established in clinical trials:	
FREEDOMS, N=1033, vs. placebo	
– ARR reduced	Bradycardia, AV block
– EDSS at 2 years reduced	Hypertension
– risk of disability progession reduced	Macular edema
	Infections
– number of Gd+ lesions and brain-volume loss reduced	Elevated liver-enzyme levels
TRANSFORMS, N=1292, vs. IFNβ-1a i.m. (Avonex)	Reduced FEV1
Clinical experience since 2010. g.	

ARR, annualized relapse rate; EDSS, expanded disability status scale

this change stems from the alternate action mechanism. Several trials with C level evidence have been conducted in which IFNβ-1a is replaced with glatiramer acetate and vice versa. One such trial indicated that patients for whom IFNβ-1a treatment was ineffective, a switch to glatiramer acetate resulted in a significant reduction in the number of relapses[30].

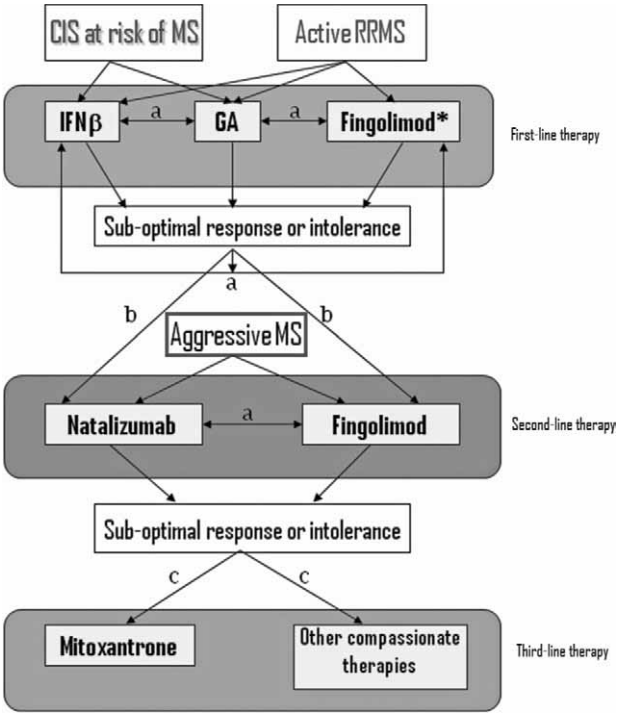

*Fig. 1. Treatment algorithm of RRMS (The Barcelona approach)[33]. In the case of suboptimal response or intolerance to first-line therapies: (a) consider switching among first-line therapies, (b) consider second-line therapies, In the case of sub-optimal response or intolerance to second line therapies: (c) consider changing to third-line therapies. *Fingolimod is approved in the USA as first line.*

Once the first-line therapeutic options are exhausted, if there is still a lack of a satisfactory response, a second-line drug should be introduced as a monotherapy. Second-line therapy should begin with natalizumab or fingolimod, while mitoxantron should remain the last possible option due to its high toxicity that limits the therapy period.

For patients with frequent relapses and constant clinical deterioration, despite first-line or second-line immunomodulation and repeated application of pulse corticosteroid therapy, the option that is applied without delay is intensive immunosuppression with cyclophosphamide or mitoxantron, or even autotransplant of bone marrow stem cells, which marks the transition into third-line therapy in escalation immunotherapy (Figures 1 and 2). In that situation of the escalation of immunotherapy, the drug that is regularly given is halted, and intensive immunosuppression begins, following a comprehensive evaluation of patient activity in order to determine the new starting position. This will enable an assessment of the response to the new therapy[31].

Several studies have shown the benefit of mitoxantrone on disease activity in patients with suboptimal response to first-line DMD[32].

Criteria of DMT Response

The therapeutic response to immunomodulation treatment can be optimal, sub-optimal and unsatisfactory. An optimal therapeutic response is seen when patients receiving basic immunotherapy show no clinical or radiological activity. These are typically called »full responders«. They remain on basic immunotherapy for as

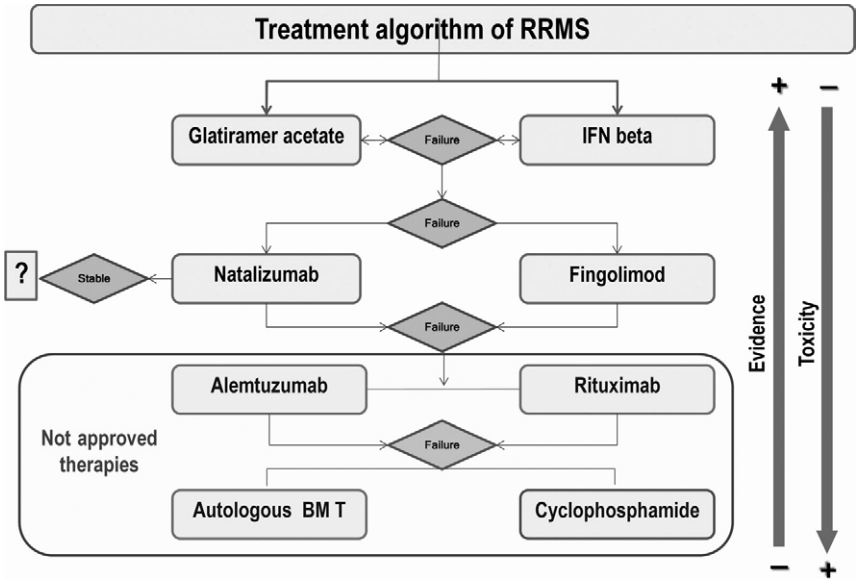

Fig. 2. Treatment algorithm of RRMS (The Latin American approach)[34]. BMT – bone marrow transplant.

TABLE 6
MITOXANTRON, BENEFIT *VS.* RISK – EVALUATION

BENEFITS	RISKS
Established in clinical trials:	
MIMS, N=194, (2002.)	Cardiotoxicity
– EDSS at 2 years reduced	Acute myelogenous leukemia
– ambulation index at 2 y. reduced	Gonadal dysfunction
– time to 1st treated relapse reduced	– female: amenorrhea
	– male: decreased sperm count
	Risk is associated with cumulative dosed!
Follow-up observational study, N=100 (2008)	(<100 mg/m^2)
Clinical experience	

long as the disease is clinically and radiologically stable. Non-responders are patients lacking a therapeutic response to basic immunotherapy, which is seen in both radiological and clinical activity. The characteristic of secondary non-responders is that there is a »breakthrough« of the disease after a varying period of satisfactory therapy response, in which the disease stagnated both clinically and radiologically. Non-responders generally require adjustment of the therapy, either within the first-line therapy, or switching to second-line therapy, depending on the level of disease activity.

The definition of a sub-optimal response to DMT is somewhat debated, considering that it implies an increased level of disease activity that can be either acceptable or not acceptable. For this reason, it is important to assess patients with a sub-optimal response to DMT to determine whether the disease activity is significant enough to require a change in the therapy by switching to a stronger but more toxic drug, or whether it is mild enough to retain the status quo. The monitoring algorithm for patients on immunomodulation therapy implies a clinical and radiological evaluation of the status in control intervals of 6 to 12 months. In the case of a stable clinical status with the absence of radiological activity, it is advised that the current therapy be continued with

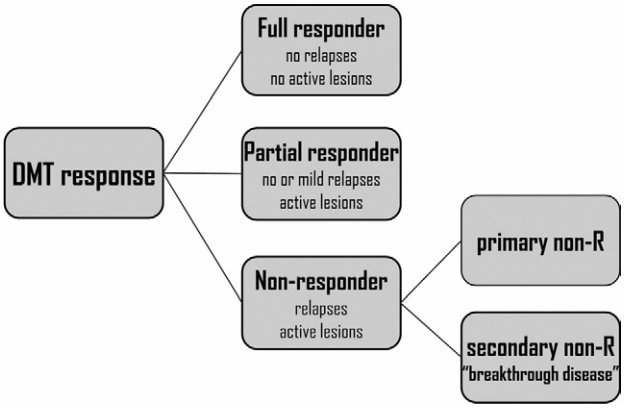

Fig. 3. DMT response.

further clinical and MR evaluations. If the control MR exam confirms radiological activity with greater than two active lesions, it is necessary to determine whether the lesions are »clinically mute« or whether the radiological activity is accompanied by clinical activity as a relapse of the disease or progression of neurological disability. The appearance of clinically mute active lesions does not require a change to the DMT, but instead only clinical monitoring with frequent clinical and MR assessments. On the contrary, the appearance of radiological activity accompanied by clinical activity requires a change in the DMT. Sub-optimally controlled MS with an unacceptable increase in the disease activity level requires a change in therapy. It should be stressed that for now, there are no testing results with a first degree proof level that would support the application of escalation immunotherapy in patients with a sub-optimal response, therefore, it is necessary to bear in mind that any decision made in that stage of the therapeutic algorithm will be based on less concrete evidence that those made at the start of treatment. Keeping these limitations in mind, the approach in selecting the optimal strategy should, above all, be individual, based on the age at which the disease began and the level of disease activity during basic therapy, and also on the different mechanisms of drug activity.

Induction Therapy

The concept of escalation therapy has both advantages and disadvantages. The advantages of this strategy are that the treatment begins with immunomodulation drugs with the most favourable risk-benefit ratio. This implies good tolerance of the treatment, without significant adverse reactions. However, the lack of this strategy is that it most often does not ensure optimal disease control. It would be excessive to expect that the basic immunotherapy can fully halt disease activity. The state in which the disease is active and sub-optimally controlled, despite the immunomodulation therapy, increases the risk of lasting neurological disability. Recognition of a

TABLE 7
INDUCTION THERAPY – ADVANTAGES AND DISADVANTAGES

Advantages	Disadvantages
Early and powerful immunosuppressive efect.	Toxicity
	Infections
»Reset« of the immune system to prevent epitope spreading and control inflammatory disease activity more effectively than immune modulation.	Malignancy
	Leucopenia
	Infertility, amenorrhea
	Cardiomyopathy
	…
Prevention of early irreversibile damage.	Suppression of protective autoimmunity
Better risk/benefit ratio when started early for a short period of time.	Inhibition of remyelination
	Remyelinating Ab's
	Scavenger macrophages

TABLE 8
CLINICAL AND MRI PROGNOSTIC FACTORS IN EARLY MS

BETTER PROGNOSIS	POORER PROGNOSIS
Monofocal onset	Multifocal onset
Onset with optic neuritis or isolated sensor symptoms	Onset with motor, cerebellar, or bladder/bowel symptoms
Low relapse rate in first 2–5 years	High relapse rate in first 2–5 years
Long interval to 2nd relapse	Short inter-attack latency
No or low disability at 5 years	Disability at 5 years
Low lesion load on MRI	Abnormal al MRI ≥2 contrast Lesions ≥9 T2 lesions

suboptimal response to therapy and the timing and choice of therapy switches in patients with breakthrough disease remain challenging for clinicians who treat MS patients. An alternative to escalation strategy, the concept of induction therapy is recommended for patients with more aggressive disease and implies short-term intensive immunosuppresive therapy as the initial therapy followed by long-term maintenance therapy with an immunomodulatory drug. Early immunosuppression might control inflammatory disease activity in RRMS more effectively than immunemodulation and therefore could better preserve brain function and control disease progression. The advantage of early immunosuppressive therapy is actual the »resetting« of the immunological system to prevent irreversibile damage and the phenomenon of epitope spreading among others which results in better control of disease activity. Ultimately, this prevents early irreversibility of damage.

Induction therapy, however, has disadvantages that can be potentially risky for patients, primarily due to the increased toxicity of immunosuppressive therapy. This pertains to the increased risk of infection and malignance, followed by leukopaenia, gonadal dysfunction and cardiomyopathy. Immunosuppressive therapy can have an undesirable inhibitory effect on remyelinisation.

Considering the potential risk of induction therapy, it must be carefully planned. It is most important to properly select patients who are potential candidates for this therapeutic approach, based on the clinical and radiological prognostic risk factors of early neurological disability. The clinical parameters that can have a predictive value in early phases of MS, as they enable identification of patients with a likelihood of poor disease outcome, are: multifocal start of the disease with symptoms of motor and sensory deficiency and a loss of sphincter function with incomplete recovery after the first episode, followed by a high relapse rate and short inter-relapse interval, and the development of neurological disability within the first five years. The MR prognostic factors of a poor disease outcome are a large number of lesions with persistent radiological activity, and the presence of lesions in the infratentoral and spinal regions.

Those patients presenting with several of these clinical and radiological features are likely to be at higher risk for early disability, either secondary to accumulating relapse related disability or earlier evolution into the secondary progressive MS stage[35]. Different prognostic factors in early MS are summarized in Table 8[36,37].

Patients transitioning to more progressive disease may be nearing the end of the window of opportunity for immunomodulatory treatment and may require intervention with more aggressive agents[38]. Mitoxantrone is approved for worsening RRMS and should be considered in such patients given its proven efficacy for reducing disease activity in this patient population.

Conclusion

Considering that the currently available basic immunotherapy is only partially effective, and that in a share of patients, the disease progresses despite treatment, the question arises as to which therapeutic approach is the right one in treating RRMS – escalation or induction? Both treatment strategies may be valuable options, in which the concept of induction therapy is recommended for patients with a more aggressive form of the disease which already presents a high relapse rate with multi-focal onset and rapid development of neurological disability even in the earliest phases. The current escalation approach in active MS may leave patients with suboptimal disease control for several years before treatment is advanced to more potent agents. This may lead to a missed window of opportunity to prevent permanent disability resulting from irreversibile axonal loss.

Starting the most effective treatment initially and move into well-tolerated maintenance when disease activity is controlled may be a better approach. This treatment concept is potentially more risky for the patient due to the possible serious adverse reactions from immun osuppressive therapy. However, it represents the strategy of choice in aggressive forms of MS where conversion into the secondary progressive form of the disease can be expected very early, which narrows the possible treatment for these patients.

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B. Nevajda

University of Zagreb, University Hospital Dubrava, Department of Neurology, Avenija Gojka Šuška 6, 10 000 Zagreb, Croatia
e-mail: bnevajda@zvu.hr

TREBA LI MULTIPLA SKLEROZA BITI TRETIRANA ESKALACIJSKOM ILI INDUKCIJSKOM TERAPIJOM?

S A Ž E T A K

MS je kronična, progresivna bolest čiji dugoročni ishodi determiniraju ključne društvene, medicinske i gospodarske utjecaje ove bolesti. Terapije za modificiranje bolesti (DMT) za multiplu sklerozu su pripisani za odgađenje progresije bolesti i za zaštitu pacijentove funkcionalne sposobnosti. Pojmovi eskalacije i indukcije imunoterapije kod MS predstavljaju različite terapeutske strategije za liječenje MS-a. Obje strategije mogu biti vrijedne opcije za pacijente koji počinju sa DMT terapijom, no indukcijska terapija se usredotočuje na pacijente sa vrlo agresivnim tijekom MS-a. Koristeći pristup jedinstven pojedinom pacijentu za odabir liječenja, MS može biti učinkovito kontrolirana bolest i može odgoditi ili čak spriječiti razvoj sekundarno progresivne MS.