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ORIGINAL COMMUNICATION

Multiple Sclerosis Therapy Consensus Group (MSTCG)

Basic and escalating immunomodulatory treatments in multiple sclerosis: Current therapeutic recommendations

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Abstract This review updates and extends earlier Consensus Reports related to current basic and escalating immunomodulatory treatments in multiple sclerosis (MS). The recent literature has been extracted for new evidence from randomized controlled trials, open treatment studies and reported expert opinion, both in original articles and reviews, and evaluates indications and safety issues based on published data. After data extraction from published full length publications and critically weighing the evidence and potential impact of the data, the review has been drafted and circulated within the National MS Societies and the European MS Platform to reach consensus within a very large group of European experts, combining evidence-based criteria and expert opinion where evidence is still incomplete. The review also outlines a few areas of controversy and delineates the need for future research.

Key words Multiple Sclerosis · immunotherapy · randomized trials · monoclonal antibodies · interferon β · glatirameracetate · treatment escalation

Introduction

Since the last consensus recommendations on immunotherapy of multiple sclerosis (MS) in 2002, issued by the Multiple Sclerosis Therapy Consensus Group (MSTCG), the group expanded to include further European countries. This led to the publication of a first multinational English language consensus report with the contribution of other European authors in 2004 [1]. Recently, members of the MSTCG (Austria, Switzerland, and Germany) also published evidence-based consensus recommendations for symptomatic therapy of MS [2]. The aim of these reports is not to simply review all available treatments but rather to summarize our current understanding of immunomodulatory treatments. Evidence-based material and, where evidence is still lacking, expert opinion form the basis of these evaluations. In the end, recommendations are outlined that may guide physicians and patients in an unbiased fashion when selecting treatment options. By way of regular updates these reports are meant to present the state-of-the-art information on these issues. It has been the declared opinion of the MSTCG to not include recommendations of drugs under trial as long as the data have not been made available in detail for peer review or published in a scientific journal. Off-label compounds are not excluded from the report as long as published material and expert opinion support their therapeutic role in certain situations that are encountered in daily practice.

The present report on immunomodulatory therapy of MS, issued by the MSTCG, is understood as an update of the existing publications. Most recommendations made earlier by the MSTCG on the use of disease modifying drug (DMD) therapy remain valid. Some modifications, based on new insights from current study results, are detailed below. Formally, the evidence-based recommendations are derived from the recognized cri-

teria defined by the American Academy of Neurology (AAN) [3], as already outlined in the previous publications.

The following topics are covered in this update:

- Modified diagnostic criteria for MS
- Current evaluation of interferon-β preparations
- Current evaluation of glatiramer acetate
- Benefits and risks of natalizumab (Tysabri®) therapy
- Use of other immunomodulatory therapeutic strategies
- Initiation and duration of immunotherapy

Modified diagnostic criteria for MS

Due to widespread use of the new diagnostic criteria for MS [4] published in 2001, their sensitivity, specificity and practicability can now be better estimated [5, 6]. The starting point for the diagnostic approach to and definition of MS remains exclusion of disorders that could better explain neurological symptoms and signs. Delineation of new diagnostic criteria, now generally referred to as the "McDonald criteria", was prompted by the recognition of MRI as the most important paraclinical diagnostic tool and the need to establish diagnosis early with high accuracy given the first time availability of DMD therapies. The authors clearly identified the requirement for prospective assessment of specificity and sensitivity as well as the predictive power of these criteria. Appropriate studies were carried out and yielded pertinent results that allowed simplifying of the MRI criteria for dissemination in time. Furthermore, spinal cord imaging was included in the diagnostic algorithm. Finally, criteria for primary progressive MS were modified [7]. These changes formed the basis for the revised criteria published in 2005 (Table 1) [8].

Consequently, according to this international consensus CSF analysis is not required to establish the diagnosis. We hold the opinion, however, that CSF analysis is still highly recommended ("expert opinion") to confirm MS and exclude other diseases.

In patients who experience an initial clinical event suggestive of MS (clinically isolated syndrome, CIS), a complete diagnostic work-up is still needed before the revised "McDonald criteria" are applied. This includes a complete history with specific questions concerning autoimmune diseases (including a family history), laboratory chemistry including lumbar puncture with confirmation of an inflammatory CSF syndrome (oligoclonal IgG bands in CSF or quantitative confirmation of intrathecal IgG synthesis). This clarification is used in particular to differentiate and exclude other autoimmune diseases with possible CNS involvement, including vasculitis, paraneoplastic syndromes, or confirmation of chronic infections.

If the revised diagnostic criteria are applied consistently, it is possible to increase evidence for temporal and spatial dissemination on MRI and thus reach a diagnosis of MS as early as 31 days after the first clinical symptom [9].

The current view holds that no specific laboratory parameter exists to assess the risk of developing MS after a first suggestive clinical event or predict the further course of the disease at an early stage. The possible prognostic significance of antibodies to components of the central myelin (e.g. to myelin basic protein, MBP, and myelin oligodendrocyte glycoprotein, MOG) is currently the subject of numerous investigations. Initially, one study indicated a high predictive value of these antibodies for the risk of a second relapse following CIS [10]. In another study, raised IgG antibody titers to MOG were found during MS relapses and in secondary progressive MS [11]. However, these specific findings were not confirmed in other MS populations [12–15]. Therefore, presently there is no role for such assays to estimate the

Table 1 Extended definitions in the updated "McDonald criteria"

Relapsing-remitting course
The following additions to the original criteria were proposed to confirm spatial dissemination on MRI:
– A spinal lesion is equivalent to an infratentorial cerebral lesion.
– A spinal lesion with gadolinium contrast enhancement may replace a cerebral lesion that accumulates contrast agent.
– Spinal and cerebral lesions can now be added to yield the required total number of 9 lesions.
The following additions were proposed to confirm temporal dissemination on MRI:
– new T1 lesion with contrast enhancement in a MR scan obtained after 3 months, occurring outside of those CNS regions likely to have been responsible for the initial clinical symptoms and signs
– new T2 lesion at any time compared to a reference MR scan carried out at least 30 days after the onset of the initial clinical event
Primary progressive course
Continuous progression of neurological symptoms over a period of 1 year plus 2 of the 3 following criteria:
– 9 cerebral T2 lesions or 4 cerebral lesions and pathological VEP
– 2 focal spinal T2 lesions
– pathological cerebrospinal fluid (CSF) findings (oligoclonal IgG bands in CSF or quantitative proof of intrathecal IgG synthesis)

risk of converting to MS after CIS, to predict the course of the disease or to guide any therapeutic decisions. It should be kept in mind that no definitive marker exists to predict long-term disability outcome in MS at the present time, and more research is needed using a panel of potentially relevant biomarkers.

Recently, antibodies to the widely distributed water channel protein, aquaporin-4, present also on astrocytes, have been suggested as a diagnostic marker in patients with neuromyelitis optica (NMO, Devic's syndrome) [16, 17]. The existence of these antibodies in patients with NMO and longitudinally extensive transverse myelitis (LETM) has been confirmed by independent workgroups [18, 19]. The question whether measurement of these antibodies might serve as a suitable marker for monitoring disease activity and treatment response in patients with NMO is currently under investigation. This assay gains importance since it may represent the first surrogate marker linking clinical aspects with antibody-associated disease mechanisms described by histopathology [20]. In typical MS, these antibodies appear to be absent, suggesting that NMO and LETM represent a different disease entity.

The extent to which evoked potentials could be used as prognostic markers in the early phase of the disease is still under discussion, as demonstrated in recent publications [21, 22]. It seems that the utility of evoked potential testing in the diagnostic work-up and management of MS patients is viewed differently between European MS specialists

Current evaluation of interferon-β preparations

The approval of three recombinant interferon-β (IFN-β) preparations, Betaferon/Betaseron® (Berlex-Schering/BayerVital); Avonex® (Biogen Idec) and Rebif® (Merck-Serono), for treatment of relapsing remitting MS was granted after evidence-based efficacy was documented in class I studies in specific dosages and forms of application. On the basis of the two-year data from the BENEFIT study [23], Betaferon® (IFN-β1b) was recently approved for use in "patients with an initial demyelinating event and high risk of occurrence of clinically definite MS" by the EMEA (European Medicines Agency). Avonex® (IFN-β1a) has also received approval for early therapy with the same restrictions. Rebif® (IFN-β1a) was recently approved by the EMEA for treatment of MS according to the McDonald criteria, expanding the previous situation where clinically confirmed MS (according to Poser criteria) was required for on-label use [24].

Further analyses of the BENEFIT study after three years (every patient on treatment for at least 12 months) demonstrated a superior effect of early treatment with IFN-β on disease progression as measured by the EDSS in this cohort of CIS patients [25]. Long-term studies with duration of up to 16 years are now on file for all three IFN-β preparations, demonstrating that in the course of treatment no novel severe side effects were documented, supporting previous evidence that safety is also confirmed over long treatment periods [26, 27]. A number of retrospective follow-up observations suggest continued efficacy of the IFN-β preparations in long-term use, with the known inherent limitations of retrospective analyses and extension studies.

Initial observations in patients with childhood MS demonstrate that IFN-β preparations appear to be safe also in this age group as long as liver enzymes (transaminases) are within the normal range – at least over an observation period of two years [28–31]. In some countries these data resulted in extended approval for IFN-β also for patients below age 18.

Several reports of pregnancies occurring during therapy with recombinant IFN-β preparations raised the point that there may be a moderate, but not statistically significant increase of the risk of early spontaneous abortions and low birth weight [32, 33], so their use is not recommended during pregnancy. Above all, effective contraception should be encouraged, since in the referenced studies adverse events occurred despite early discontinuation of IFN-β medication after a positive pregnancy test. However termination of pregnancy is not indicated.

As pregnancy itself is regarded an "effective immune intervention", a careful risk reduction analysis in any female patient planning pregnancy should be performed. Depending on disease activity, IFN-ß may be given until initiation of pregnancy, but should not be administered while being pregnant or during breast feeding (see also section on Use of other immunomodulatory therapeutic strategies).

During pregnancy, any treatment other than glucocorticosteroids after the first trimester remains an off-label option even for marketed compounds.

Clinical studies of subcutaneously (s.c.) applied IFN-ß preparations (Rebif® and Betaferon®) revealed a dose- and frequency-dependent efficacy with several applications per week [reviewed in 1, 3].

However, no dose-efficacy relation was demonstrated in a class I evidence comparison of Avonex® (30 µg vs. 60 µg intramuscularly [i.m.] per week) in relapsing MS [34, 35]. Also, with once weekly application of Rebif®, no difference was determined between 22 µg and 44 µg s.c. per application [36].

Comparative studies

Among the direct comparative studies of IFN-β preparations for relapsing MS published to date [37], only three studies meet the criteria for class I evidence [3]. In the first head-to-head trial, the EVIDENCE study, Rebif®

(3 × 44 µg/week s.c.), was tested against Avonex® (1 × 30 µg/week i.m.) for a difference in efficacy defined as the risk for new relapses: Rebif® was significantly more effective than Avonex® in terms of relapse rate, time to next relapse and MR activity [38], with differences still detectable after 16 months [39]. On the other hand, disease progression as a reflection of increasing disability (measured by Kurtzke's EDSS) did not differ significantly between the two treatment groups, but the study was not sufficiently powered to show this. In patients who, after conclusion of the comparative study or at the end of the core study, switched to high-dose therapy with Rebif® 3 × 44 µg/week, the relapse rate was significantly reduced in the further course [40]. On the other hand, the results of this follow-up study are somewhat limited for a number of very relevant methodological reasons. Importantly, patients and treating physicians were no longer blinded after switching therapy.

In a second comparative trial, the INCOMIN study, Betaferon® in the standard dosage of 250 µg s.c. every other day was compared to Avonex® 30 µg i.m. once a week over a period of two years, randomized in a design that was open-labeled to patients and examining neurologists [41]. MRI evaluation was performed centralized in a blinded fashion. Under Betaferon® treatment, a larger number of relapse-free patients and a lower rate of new lesions on cranial MRI were detected as compared to Avonex®. One problematic aspect of this study is that the examining neurologists were not blinded as to the applied medication, so that one of the important quality standards for treatment trials in MS was not met.

In the third study, Betaferon® was also compared prospectively in an open, randomized design with Rebif® 22 µg s.c. once weekly [42]. No significant differences between the two therapeutic regimens were determined for the relapse rate at 24 months or the time to first relapse under medication.

Three other studies have been completed recently and were reported at international meetings. According to the policy of the MSTCG reports, the readers are encouraged to critically check the study design and results in the upcoming publications. In the BEYOND study, two higher doses of IFNβ-1b were tried and found to be not more effective than the licensed dose. Two recent trials compared IFNβ-1b (Betaferone) and copaxone and IFNβ-1a (Rebif 44), the BECOME and the REGARD studies, respectively, and the presented data point to a similar degree of efficacy.

Significance of neutralizing antibodies

The formation of neutralizing antibodies (NAB) under medication is of concern, because this may be associated with loss of efficacy, at least in patients with persistently high titers of NAB.

The frequency of NAB differs between the three IFN-β preparations (with Avonex® less than Rebif® and Betaferon® [43, 44]). In the first two years of treatment, the risk of NAB formation is relatively high [45]. An independent study of Danish MS patients showed that the frequency of relapses in patients with high-titer NAB during IFN-ß therapy is increased [46]. Further evaluations of the pivotal, approval-relevant therapeutic studies also indicated that the risk of therapy failure increases in the presence of continuously high NAB titers [47–49]. However, the longitudinal analyses of NAB positivity in the BENEFIT trial did not show a correlation between outcome (EDSS) and NAB in the three-year analysis [50].

Since the occurrence of NAB was not regarded an important issue for treatment success for a considerable time period, no systematic studies were carried out to address this specific point. In addition, there are studies investigating therapeutic methods aimed at the reduction of NAB [46]. Such approaches are known in principle from other areas of clinical medicine. Initial studies are now underway considering therapeutic modulation of NAB formation. The quantification of NAB, and thus its relevance to individual therapeutic decisions, is only feasible by using standardized, generally acceptable testing methods [51]. Within the framework of an EU project, such analytical methods are currently being developed, improved, standardized, and finally clinically validated for large patient cohorts at a number of European MS centers.

The recommendations already issued by a working group of the European Federation of Neurological Societies (EFNS) on regular monitoring of NAB in the course of treatment with recombinant IFN-β [46] may be subject to amendments once proper prospective trial are published and these issues are definitively settled. Moreover, further methodological work is to be completed, and if the hypothesis is supported by further data, regular NAB measurement may be implemented on a larger scale.

Current recommendations

Based on the studies on file, the following recommendations currently apply to the use of IFN-ß preparations in MS (Table 2).

Current evaluation of glatiramer acetate

Long-term data on glatiramer acetate (GA, Copaxone®) injected daily s.c. with follow-up periods of up to ten years revealed no unexpected new adverse effects and favor early initiation of treatment [52, 53]. Regarding the efficacy of Copaxone® in comparison to recombinant

Table 2 Recommendations for the treatment of MS with IFN-β

- No consensus has been reached yet as to whether a high-frequency strategy should be used primarily if the decision is made to use IFN-β.
- Determination of NAB is recommended if treatment failure is suspected.[1]
- If high-titer NAB are measured at least twice (according to standards of the individual laboratory), IFN-β therapy should be discontinued and a different therapeutic approach should then be initiated.
- In cases of clinically confirmed treatment failure, it is not necessary to wait for the second NAB test before switching to another immunomodulating therapy.
- Currently, there are no proven strategies available that effectively and persistently reduce NAB.

[1] Due to the nature of the consensus, there are some deviations from some recommendations published elsewhere by some of the co-authors of this report [46]

IFN-β preparations, several open-label follow-up observations are on file. The first prospective trial including this comparison has not yet been published as a full length paper (BEYOND trial).

The available observations suggest good tolerability [54, 55] and claim no major difference in efficacy as compared to that of the IFN-β preparations when used in the relapsing-remitting course [52, 53]. The option of switching from recombinant IFN-β preparations to Copaxone® in case of intolerance or therapy failure with repeated measurement of high NAB titers received a positive evaluation in an open monitoring study [55]. A randomized, placebo-controlled study to investigate efficacy of Copaxone® in clinically isolated syndrome has been reported at meetings but is not yet published as a full length paper (PreCISe trial).

Initial clinical data are on file pointing towards a dose-effect relation with Copaxone®: In a phase II study, it was suggested that a dose of 40 mg daily may be more effective than the standard dose of 20 mg but primary endpoints were not met [56]. In an initial de-escalation study, it was shown that glatiramer acetate can be used safely following mitoxantrone treatment and may have an effect on prolonging mitoxantrone-induced remission in terms of relapse rate [57].

Investigating the proposed mechanism of action of GA, evidence is accumulating that the induction of neurotrophic factors could play an important role [58]. Despite interesting findings in experimental models of MS and in vitro [59], the evidence of a neuroprotective or neuroregenerative effect of Copaxone® in patients is limited. Further, no convincing data that demonstrate major differences with regard to such parameters in comparison to Interferons [60] are available. No effect was observed in a clinical trial of GA in patients with PPMS [61]. A possible effect may have gone unnoticed by the unexpectedly slow progression in the placebo arm of that trial. One study using oral administration of GA yielded negative results [62].

Benefits and risks of therapy with natalizumab (Tysabri®)

The development of humanized monoclonal antibodies that specifically block molecules relevant for the pathogenesis of a given disease has greatly expanded current treatment options and has added new therapeutic potential for numerous neoplastic and chronic inflammatory diseases.

The first successful example of such a designer drug in the treatment of relapsing MS is natalizumab (Tysabri®, Biogen Idec/Elan). This is a humanized monoclonal antibody directed against α4-integrin, a component of VLA-4 (very late antigen-4) present on leukocytes. Binding of natalizumab to VLA-4 blocks its interaction with the ligand VCAM (vascular cell adhesion molecule) on the surface of endothelial cells at the blood-brain barrier, thus greatly reducing the transmigration of lymphocytes and monocytes from venules and capillaries into inflamed tissue [63, 64]. Targeting this molecular interaction with a monoclonal antibody was proven effective in diminishing disease activity in earlier studies in the animal model [65, 66].

In view of the promising results of a phase IIb trial showing a significant reduction of active lesions on MRI under monthly natalizumab infusions [67], two large phase III trials with natalizumab were carried out in relapsing-remitting MS. The first study compared natalizumab vs. placebo (AFFIRM) and the second natalizumab plus Avonex® vs. placebo plus Avonex® (SENTINEL). In both trials, a marked and statistically significant superiority of natalizumab (300 mg once every four weeks intravenously) was demonstrated for the monotherapy and combination therapy on primary and a number of secondary endpoints [68, 69]. During the two-year trial phase, it was observed that twice as many patients experienced no disease activity at all (no relapses, no EDSS progression, no new MRI activity as measured by T2 and T1 lesions) on natalizumab in comparison to placebo. Convincing data on relapse rate reduction after one year in the AFFIRM study resulted in accelerated approval of the agent in the US at the end of 2004.

Only three months later, sale of the preparation was

put on hold by the manufacturer, when progressive multifocal leukoencephalopathy (PML) was diagnosed in two patients from the SENTINEL trial and in one patient with Crohn's disease (CD) who had received natalizumab within the framework of a different trial. Two patients died of PML and the third survived with severe residual defects. Extensive investigations, aimed at clarifying the causal connection between treatment with natalizumab and the occurrence of this severe opportunistic infection, have not yet revealed a convincing explanation [70]. A detailed follow-up investigation (including cranial MRI and CSF analysis) of the patients who received natalizumab in trials of MS, CD and rheumatoid arthritis reassuringly revealed no further cases. Results are listed in Table 3 [71].

Restricted approval

In addition to these three cases of PML, further opportunistic infections are listed to have occurred on therapy with Tysabri® in the current extended information for physicians (in some cases also with monotherapy) [74]. Following submission of additional safety data, the EMEA has issued approval of natalizumab for treatment of relapsing MS with a number of restrictions (http://www.emea.eu.int/humandocs/Humans/EPAR/tysabri/tysabri.htm). The preparation has been available in the EU since July of 2006. According to the current scientific information, natalizumab (Tysabri®) is indicated as a "disease-modifying monotherapy of highly active relapsing MS" for the following patient groups [75]: 1) patients showing high levels of disease activity despite treatment with an IFN-β preparation, or 2) untreated/treatment-naive patients with rapidly progressing relapsing-remitting MS (at least two serious relapses per year).

The approval label currently represents a compromise between the expected benefit and the potential risk of this therapy, with emphasis on the greatest possible patient safety. However, the current approval indications do not reflect significant portions of the inclusion criteria applied in the two phase III trials (AFFIRM and SENTINEL). Under the approval conditions now in force, Tysabri® can therefore be considered as a preparation for escalation therapy in relapsing MS without signs of secondary progression, but with insufficient efficacy of baseline therapy with IFN-β or glatiramer acetate. According to the MSTCG recommendations, only mitoxantrone had filled this slot to date [1]. However, this drug also involves a total risk of severe side effects in about 0.2–0.4 %, (cardiomyopathy and medication-associated leukemia, even before the cumulative dose level is reached [76–78], during or following therapy [79]). Tysabri® therefore represents, according to current data, an alternative monotherapy in escalation treatment of relapsing MS. Of note, Tysabri® is not labeled for use in relapsing-progressive disease (SPMS with superimposed relapses). It must not be combined with other immunomodulatory or immunosuppressive treatments.

Specific recommendations for daily practice [80] or initiation of natalizumab following preceding immunotherapies [81] have been published.

Therapeutic recommendation

The MSTCG recommends the following procedures listed in Table 4 for the use of Tysabri® in view of the current data and EMEA approval conditions.[1]

Natalizumab (Tysabri®) as first-line therapy in patients with severely active RRMS evidenced by at least two severe relapses per year should be considered only in close cooperation with an MS center [80]. Also, the highly detailed information and recommendations in the physician information and management guidelines for natalizumab (Tysabri®) should be complied with [74]. It is another important aspect that NAB directed at natalizumab (Tysabri®) can occur in up to 6 % of patients treated with this monoclonal antibody and that high NAB titers seem to persist. This appears to be associated with reduced efficacy, and an increased risk of infusion reactions was detected. During the first few years after approval of natalizumab (Tysabri®), new in-

Table 3 Progressive multifocal leukoencephalopathy and natalizumab (Tysabri®)

- In more than 3,000 patients who had received natalizumab in trials (average treatment period 17.9 months), PML occurred only in three persons as cited in the text. (see Note added in Proof)
- The disease occurred only in patients subjected to combination therapy with natalizumab plus Avonex® (n = 2) or following previous, partly overlapping, immunosuppressive pre-treatment under monotherapy (1 patient with CD).
- The calculated risk of contracting PML is thus calculated as approx. 1:1,000 following an average treatment period of just under 18 months.
- Using a sensitive PCR analysis, no JC virus genome (PML pathogen) was found in the CSF of MS patients who had not been treated with natalizumab. Therefore, there is no per se increased risk of JC virus replication and spread in the CNS resulting from MS itself [72].

FDA and EMEA notified healthcare professionals of reports of clinically significant liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, that occurred as early as six days after the first dose of Tysabri®. Tysabri should be discontinued in patients with jaundice or other evidence of significant liver injury. Physicians should inform patients that Tysabri may cause liver injury. Furthermore, two patients with melanoma possibly associated to the treatment with natalizumab have been reported recently [73]. Thus far, incidence is not higher than the expected risk in the overall MS population.

Table 4 Recommendations for the use of natalizumab (Tysabri®)

- The indication and application of Tysabri® should preferably be handled in an MS center.[1]
- Depending on the specific national situation, the initiation of natalizumab (Tysabri®) would also be feasible outside clinical MS centers if emergency services for treatment of allergic and anaphylactic reactions are established and if standardized MRI diagnostics can be realized.
- Documented patient information should be available concerning the risks peculiar to this therapy.
- It should be used as monotherapy only, in approved dosages and application intervals in immunocompetent patients (normal differential blood count and exclusion of infection) and if therapy with recombinant IFN-β (or glatiramer acetate) has failed.[2] There should be a therapy-free interval of at least 14 days before the first dose of natalizumab (Tysabri®) according to current expert opinion.[3]
- Patients with RRMS not responding to immunosuppressive drugs can be switched to natalizumab (Tysabri®) after considering the risk-benefit ratio and only after at least a 3-month drug-free interval following azathioprine-equivalent drugs and after a much longer interval (up to 6 months) following mitoxantrone (expert opinion).[3] However, no definitive data are available yet on the safe time intervals.
- Before initiation of therapy, the diagnosis of MS must be established. A baseline reference cranial MR scan is obligatory, which also helps to rule out other non-MS disorders, in particular when "atypical MS lesions" are seen.[4]
- Quarterly neurological checkups in MS centers, with particular attention paid to cognitive and neuropsychological functions (e. g. aphasia, apraxia, cortical blindness as possible evidence of PML), should be performed.
- If PML is suspected (clinical or MRI-based according to established guidelines), natalizumab (Tysabri®) therapy should be interrupted, followed by cranial MRI and lumbar puncture to confirm or exclude JCV infection by DNA testing. If PML is suspected but PCR is negative, a cerebral biopsy may be considered.

PML progressive multifocal leukoencephalopathy; *DNA* desoxyribonucleic acid, MRI magnetic resonance imaging

[1] Regular procedure in Austria.

[2] Glatiramer acetate is, according to the MSTCG, a baseline therapy comparable to the IFN-β preparations. For no apparent reason, it was not mentioned in the EMEA approval for natalizumab (Tysabri®).

[3] Although there are no clinical data on wash-out periods after the use of any immunosuppressive drug, a delayed initiation of natalizumab seems reasonable to allow the immune system to reset. The length of the interval is arbitrary and may be subject to amendments once more information becomes available. Recently, guidelines have been discussed by an expert panel in France.*

[4] Some centers recommend CSF analysis prior to therapy so that a specimen of baseline CSF can be stored for comparison with subsequent examinations.

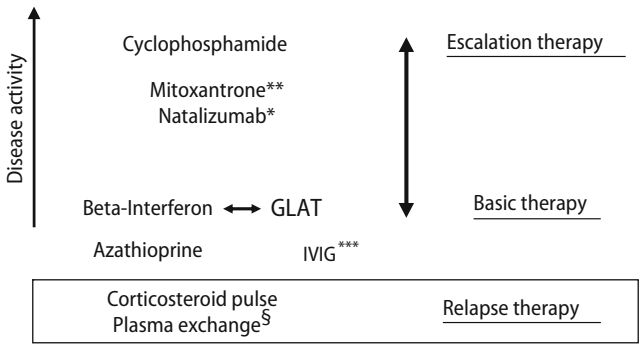
* Beyond the usual precautions for the use of monoclonals it is recommended (this is now mandatory in France) to formally exclude latent tuberculosis (by chest x-ray and tuberculin testing, particularly in patients coming from high-risk populations) and any ongoing opportunistic infection including HIV, PML, and to test for signs of immunodeficiency by enumerating CD 4+ and CD 8+ T lymphocytes, and B lymphocytes

sights can be expected and this may result in a revised estimation of the risk-benefit ratio for this therapeutic antibody. Indeed, at the request of the approving agencies, the manufacturers have set up an extensive pharmacovigilance and risk management program. Physicians planning to prescribe natalizumab (Tysabri®) should therefore check up on such new data at regular intervals [81] (see Note added in Proof).

Natalizumab (Tysabri®) was also studied for the treatment of acute MS relapses in a limited number of patients, but a single i.v. application of this monoclonal antibody had no significant effect on alleviation of relapse symptoms [82]. Therefore, at present high-dose glucocorticosteroids remain the only relapse therapy that can be recommended (Fig. 1). Only in cases of severe steroid-resistant symptoms may repeated pulse treatments with corticosteroids be followed by plasmapheresis.

Open questions

There are several open questions concerning natalizumab (Tysabri®) that have not yet been answered but need to be clarified within the framework of appropriate prospective studies, some of which are ongoing (Table 5).



* In cases of ≥ 2 severe relapses per year it may also be used as basic therapy
** Change of these therapies at this stage of escalation not yet formally evaluated
*** Considered in some European countries as second line treatments but not indicated in France
§ Option in severe, steroid-resistant relapses

Fig. 1 Escalating immunotherapy of RRMS (update 2008)

Use of other immunomodulatory therapeutic strategies

The development of new immunomodulators for MS therapy has made considerable progress in recent years. Currently, several substances that have successfully completed phase II trials are being investigated in approval-relevant, large-scale, randomized and placebo-controlled phase III studies. Examples include teriflunomide [83], Fingolimod (FTY 720) [84], Laquinimod,

Table 5 Open questions in the treatment with natalizumab (Tysabri®)

– incidence of PML under monotherapy with natalizumab (Tysabri®), including risk factors and diagnostic methods
– development of early predictors for the therapeutic response
– evaluation of the necessary and optimum duration of treatment
– evaluation of appropriate escalation treatments after stopping natalizumab (Tysabri®) (e. g. because of failure or intolerance) and of modes to de-escalate from mitoxantrone to natalizumab (Tysabri®)
– other and potentially relevant mechanisms of action that are independent of adhesion molecule blockade at the blood-brain barrier
– establishment of practicable methods to define immunocompetence before and during therapy with natalizumab (Tysabri®)
– response rates and risks of immunizations under natalizumab (Tysabri®) treatment
– effects of natalizumab (Tysabri®) during pregnancy and breast feeding
– frequency of neutralizing antibodies to natalizumab (Tysabri®) and their clinical effects
– validation of test method to detect NAB to natalizumab

BG-12 and cladribine [85]. Oral formulations of these substances are currently undergoing approval-relevant testing in phase III trials. Results of these trials are not expected before 2009.

Furthermore, the monoclonal antibodies anti-CD52 (Alemtuzumab), anti-CD25 (Daclizumab) and anti-CD20 (Rituximab) have been studied with encouraging data in Phase I and II trials, partly published to date [86–93]. Phase II and III trials with these agents are running. These antibodies are approved in other indications, e.g. rheumatoid arthritis, transplantation or different neoplastic disorders; therefore off-label use would be possible in MS. Alemtuzumab seems to have high anti-inflammatory potential, but a considerable risk of opportunistic infections or occurrence of other autoimmune disorders (thyroid autoimmunity, idiopathic thrombocytopenic purpura). The occurrence of PML has also been described with relation to therapy with Rituximab in patients with SLE.

Since the most recent publication on recommendations for stage- and severity-adjusted immunotherapy by the MSTCG in 2002, there are still no data from trials available investigating this concept in a formal manner. Therefore the principle of this concept must still be considered as class III evidence. Investigations on the combined use of IFN-β and immunosuppressant drugs, e.g. azathioprine [94, 95] or methotrexate [96], were carried out but only the target parameter "tolerance" has successfully been investigated. No clinical efficacy data for a period longer than one year have been published as yet [97]. Similarly, add-on therapy with cyclophosphamide [98] and mitoxantrone [99] still has not been satisfactorily been investigated. In a small, open-labeled trial with parallel administration of either mitoxantrone or cyclophosphamide, the two medications were observed to have about equivalent efficacy on clinical and MRI parameters in SPMS patients but the statistical power of the study was low [100].

Intravenous immunoglobulins (IVIG)

None of the marketed IVIG preparations have received approval for the treatment of MS. A meta-analysis of studies on IVIG in MS published to date [101] concluded that a positive effect on relapse rate and MR activity is likely (Class II evidence) for relapsing remitting MS but the original trials have been criticized for methodological reasons.

A randomized, double-blind, one-year study showed efficacy of IVIG after a first demyelinating event. The study carried out at a single center demonstrated that IVIG significantly extended the time interval after the first episode until onset of clinically confirmed MS and diminished lesions on MRI compared to placebo [102].

In a dose comparison study with a new, higher concentrated IVIG preparation (Gamunex®) in patients with relapsing remitting MS, neither the primary (relapse rate) nor secondary endpoints were reached. It should be noted that the negative outcome of this study is probably influenced by the very low level of disease activity in the placebo group. In two additional prospective, randomized studies (involving secondary progressive MS and acute treatment of an MS relapse), the primary endpoint in each case as well as most of the secondary endpoints of the study were also not reached [103, 104]. Evidence of a remyelinating effect of IVIG postulated on the basis of experimental findings with IgM antibodies has not been confirmed by clinical studies published to date [105]. Also, in acute treatment of an MS relapse, no additional therapeutic effect of IVIG was determined in an add-on design for steroid therapy [104].

According to the nature of the study data, which on the whole are heterogeneous and in some cases contradictory, and the unsolved question of optimal dose, intravenous immunoglobulins are currently considered to be only a second line treatment in the baseline therapy of relapsing remitting MS. This view is not shared by the French co-authors, where IVIg are not considered as a therapeutic option in RR-MS outside clinical trials.

IVIG are currently neither indicated in secondary progressive MS nor in relapse therapy.

IVIG constitute the only immunomodulatory treatment option that can be used in pregnancy. In the postpartum period, a role for the treatment with IVIG has not yet been established [106].

During the lactation period IVIG has probably little if any risks for mother and newborn if used for postpartum relapse prophylaxis. Arguments in favor of such use are provided by a retrospective study and open prospective observational studies but the data are not strong [106–108].

In women with a desire to become mothers or in proven pregnancy, it has been proposed that one could bridge the time until after delivery with intravenously applied polyclonal immunoglobulins (IVIG), in view of the known adverse events of the current immunomodulatory drugs and antibodies. There is now limited evidence from open trials that IVIG may be a safe treatment alternative in pregnancy but the evidence for any efficacy of this particular indication has still not been tested by appropriate clinical trials (e.g. [106]). During pregnancy, any treatment other than glucocorticosteroids remains an off-label option even for marketed compounds.

Mitoxantrone

Following the positive results of the MIMS study, mitoxantrone received marketing approval in 2002 with the labeled indication for treatment of "patients not requiring wheelchairs with SPMS or progressive relapsing MS … in case of failure or intolerance of a previous therapy with immunomodulators" [109, 110]. This approval text underlines that a pragmatic compromise between the results of the study and the risk potential of the substance had been reached – despite the fact that, in the MIMS study, study patients were not allowed to be included if they had received any previous primary immunomodulatory treatment.

There are no data available from controlled studies to date of further immunomodulating or immunosuppressive therapy once the cumulative limit dose of mitoxantrone is reached. Based on an individual healing approach and a carefully considered risk-to-benefit ratio, use of other immunosuppressants or immunomodulators (e.g. mycophenolate mofetil or, as one of the strongest acting immunosuppressants, cyclophosphamide) can be considered in patients if disease activity continues even during escalating immunotherapy.

In the meantime, isolated cases of severe adverse effects such as cardiomyopathy or secondary leukemias have been recognized from larger observational studies with mitoxantrone in MS (see above). The overall risk for these severe side effects ranges between 1:250 and 1:800. Therefore, a reduction of the cumulative maximum dose to 100 mg/m^2 of body surface area was recommended and labeled. Based on new scientific information now published in Germany, a continuation of treatment up to a total dose of 140 mg/m^2 of body surface area (BSA) was allowed ("on-label") if done by an MS specialist and if a stringent risk-benefit analysis and parallel monitoring of cardiac function is performed. In France, the maximal dose was set at 120 mg/m^2.

Since overt cardiac adverse effects occurred in the MIMS study under higher cumulative dose levels, the new recommendations include repeated ultrasound echocardiograms carried out before each application of mitoxantrone (http://www.fda.gov/medwatch/SAFETY/2005/Novantrone_pl_may24.pdf).It is recommended to increase the dosage to above 100 mg/m^2 body surface area only if the patient has been a responder and still has signs of active disease. It should be noted that subclinical alterations may occur at much lower total doses when using a complete echocardiographic examination [111, 112].

Use of mitoxantrone in very active ("aggressive") MS

The term "aggressive" MS is the official term used by the French regulatory authorities that approved mitoxantrone for treatment in this indication, and the definition of "aggressive" RRMS (and SPMS) is based on the protocol of the French-British Mitoxantrone trial published in 1997 [113]. "Aggressive" MS was defined as disease with 1) occurrence of two relapses over 12 months both causing residual deficits or a two-point EDSS progression during the preceding 12 months and 2) the presence of one new Gd-enhancing lesion on a MR scan performed less than three months ago. In a recent study, long-term efficacy of MTX was assessed in 100 aggressive RRMS who were treated with MTX as induction therapy monthly for 6 months and followed for up to 5 years [114]. There was a dramatic reduction in annual relapse rate but some serious adverse reactions were also noted.

Other immunosuppressive compounds

Azathioprine

A reduction of gadolinium enhancing lesions was demonstrated in a small prospective study (14 patients) about the effect of azathioprine on MRI lesions in MS in a pre/post design in 14 patients. The dosage was sufficient to reduce the white blood count. Since the study had no control group, the power was low and the statistical effect of a regression to the mean cannot be excluded [115]. Therefore, azathioprine remains to be an oral second line drug in the baseline therapy of RRMS even

though the safety of azathioprine is reasonably good [116].

In smaller studies, mycophenolate mofetil (CellCept®) has recently been tested in various neuroimmunological diseases [117]. For MS, however, the data are still insufficient to justify its use outside protocol-defined, individual treatments. Controlled studies with mycophenolate mofetil as a monotherapy or as a combination therapy together with recombinant IFN-β (or glatiramer acetate) would be desirable [118]. With mycophenolate mofetil, early signs of opportunistic infections must be monitored since reports of such infections have been published [119].

For the oral immunosuppressants such as azathioprine and mycophenylate mofetil there are no consented rules as to their indication. Some authors would recommend their use as an alternative treatment in patients unwilling to take injectable DMDs, or who do not tolerate these DMDs, or for economical reasons, but this is at best class III evidence .

Other, putatively less toxic immunosuppressive drugs (immunomodulators) for escalation therapy of MS are being developed. It is also necessary to wait for the results of studies already underway or in the planning stage.

Statins

Despite some experimental evidence for an immunomodulatory and anti-inflammatory action of simvastatin and atorvastatin, it seems not justified to simply extrapolate from animal experimentation, where higher dosage levels were tested than used in human disease. One observational study published to date on MRI activity in MS patients under therapy with simvastatin does not provide a sufficient basis for the general use of statins in MS [117]. An evidence-based evaluation of this matter must await publication of studies currently in progress.

Plasmapheresis

Plasma exchange (PE) treatment of relapses, with albumin-electrolyte solute as a replacement, has been evaluated in a single class I study for severe RRMS and in one observational study of patients with severe optic neuritis, refractory to conventional pulsed steroid therapy. Best effects were achieved when therapy was administered within 4–6 weeks after onset of symptoms [118]. Therapeutic effects typically occur after a minimum of three sessions of PE. The evidence on its efficacy is still limited. Therefore this treatment modality is still to be considered as an individual treatment decision in patients with severe, functionally disabling relapses not properly responding to corticosteroids, despite hints of evidence and encouraging theoretical considerations [119]. Plasmapheresis is not recommended as a permanent disease-modifying therapy strategy in MS patients.

Initiation of therapy and duration of immunotherapy

Early initiation of immunotherapy is warranted in view of ongoing inflammatory disease activity. The main treatment goals aim at terminating inflammation and at reducing axonal damage, which is often present early in the disease process [120]. Approval for therapy following clinically isolated syndrome has been granted for Avonex® and Betaferon®. Trials with Copaxone® and Rebif® for this indication are currently in progress or data are pending publication. The criteria recommended by the MSTCG for the early initiation of therapy after the first episode suggestive for MS are still valid [1]. It is recommended to assess subclinical inflammatory activity by a second cranial MRI in accordance with the extended diagnostic criteria as early as 2–3 months after the onset of the initial episode.

Before initiation of therapy, patients should be provided with simple and clearly understandable information regarding realistic therapeutic goals, mechanisms of action and possible adverse effects. The course of the disease must be documented before (baseline) and during therapy according to a standardized protocol (Fig. 2). To monitor the efficacy of immunotherapy and improve compliance, follow-up clinical testing should be carried out in three-monthly intervals during the first year of treatment utilizing standard MS scales.

The occurrence of further relapses within the first year, a confirmed EDSS progression as well as MRI parameters of ongoing or even increasing disease activity would be regarded as a complex sign of partial or full treatment failure. The limitations of the currently existing clinical scores to faithfully reflect disease activity at all times and the uncertainties about the discriminating power of surrogate markers (MRI and others) need to be clarified.

MRI as a potential aid to therapy

The utility of frequent MRI monitoring of disease activity and response to therapy is still unclear. In a recently published six-year follow-up study, the factors associated with a positive response to ongoing immunotherapy include two MRI criteria as readout for efficacy, a low T1 lesion volume and lack of gadolinium uptake after one year of treatment [121].

Recognition and classification of recent and older lesions on MRI form the basis of the McDonald diagnostic criteria. Follow-up examinations can then provide evi-

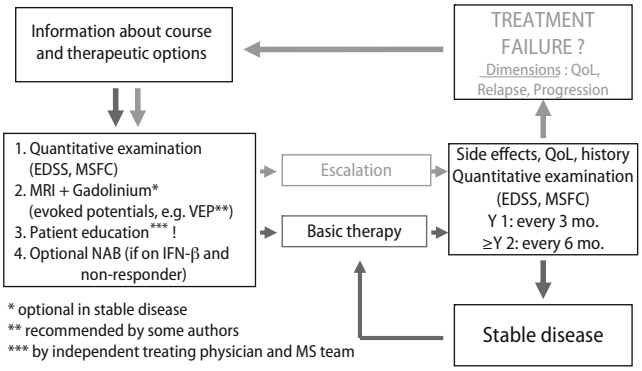


Fig. 2 Standardized algorithm to maintain disease stability in RRMS

dence of disease activity arising from new or enlarging lesions and from contrast enhancement. This information can be supplemented with magnetization transfer analyses and other more recent special techniques. Results may vary depending on the selected parameters and the procedure used. The objective of a defined MRI protocol is to reduce the methodological variability in lesion recognition which is dependent on repositioning, layer orientation, layer thickness, MR sequences, contrast agent application, and the available hardware in the technical equipment at medical institutions.

Once the diagnosis of MS has been established, repeat cranial MRI are recommended one year after initiation of therapy in stable patients by some experts but not by others (Fig. 2) to assess subclinical therapeutic effects. More information is needed to evaluate the usefulness of MRI to assess subclinical therapeutic effects in this patient group. Any serial examination should be carried out according to a fixed protocol with precise repositioning, constant layer thickness (5 mm) and layer distance with the same MR sequences and with precise monitoring of the time interval between contrast agent injection and measurement of the dose of MR contrast agent [122, 123]. If the recent medical history and the current clinical findings indicate a relevant change with new relapse activity, or if cognitive decline or other signs of clinical progression become evident, all indicating an insufficient treatment response [124], a repeat cranial and even spinal MRI should be done as an additional (surrogate) marker for disease activity and progression.

Duration of therapy

There are no controlled studies to date on the optimum duration of immunotherapy. A meta-analysis published on this subject [125] has not achieved general recognition due to methodological deficits. It is recommended to continue immunomodulatory therapy with regular neurological follow-up examinations, if:

- a therapeutic effect still appears plausible (e.g. clearly reduced number of relapses and relapse severity compared to the pre-therapeutic phase, reduced disease progression), and
- no severe side effects reduce the patient's quality of life.

It appears acceptable to gradually discontinue immunomodulatory treatment at the expressed wish of a patient after at least three years of disease stability (no relapses, no clinical disease progression, stable MRI). However, clinical follow-up and occasional MRI scans are mandatory at regular intervals over the following years in order to appreciate recurrence of disease activity.

Treatment efficacy after initiating therapy at the first demyelinating episode has to be carefully followed and evaluated. The occurrence of further relapses within the first year, a confirmed EDSS progression as well as MRI parameters of ongoing or even increasing disease activity would be regarded as a complex sign of partial or full treatment failure. The limitations of the clinical scores as to faithfully reflect disease activity at all times and the uncertainties about the discriminating power of surrogate markers (MRI and others) need to be clarified before clear-cut recommendations on treatment failure can be advocated.

The recommendations for limited application of the immunomodulatory therapy in secondary or primary progressive disease courses remain valid [1].

Note added in Proof

During treatment with natalizumab (Tysabri®), two European MS patients have been reported in a safety announcement by the manufacturer. Obviously, one of the two patients has had no other immunosuppressive medication before or during treatment with natalizumab.

These serious adverse events are currently being evaluated and the reader is referred to the upcoming bulletins.

Appendix

Multiple Sclerosis Therapy Consensus Group (MSTCG)

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