Escalating immunotherapy of multiple sclerosis

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Abstract: Basic disease-modifying treatment for relapsing forms of active multiple sclerosis (MS) is now available in many countries with high prevalence rates, for this chronic inflammatory disease of the central nervous system. Several lines of evidence support early immunomodulatory treatment with either recombinant interferon-beta or glatiramer acetate, and positive results from phase III trials encourage start of treatment even in patients with clinically isolated syndromes (CIS). However, currently available drugs for basic therapy are only partially effective and patients may still encounter relapses or disease progression. As treatment-refractory, clinically active MS can quickly lead to irreversible neurological disability there is an urgent need for effective escalating strategies. Patients with suboptimal treatment response to basic therapy have been treated with combination therapies, cytotoxic drugs (such as mitoxantrone and cyclophosphamide) or autologous hematopoietic stem cell transplantation. Recently, the monoclonal antibody, natalizumab, was added to this armamentarium. None of these strategies have been vigorously evaluated in large randomized, controlled phase III trials with patients who failed basic therapy. Therefore, the decision to escalate immunotherapy is still based on limited evidence. This article will review potential candidates for intensified immunosuppression and call for innovative study designs to better evaluate escalating immunotherapy in MS.

Keywords: immunotherapy, natalizumab, interferon-beta, glatiramer acetate, multiple sclerosis, clinically isolated syndromes

Introduction

Due to widespread application of the new diagnostic criteria for multiple sclerosis (MS) [Polman *et al.* 2005], their sensitivity, specificity and practicality are better appreciated [Dalton *et al.* 2002]. Before early disease modifying treatment (DMT) is considered it is essential to determine in which patients clinically isolated syndromes (CIS) represent early MS and to exclude disorders that could explain the signs and symptoms and mimic early disease. Early DMT is recommended in patients with CIS and a high risk of MS if evidence for subclinical disease activity is present on the brain MRI or severe relapse symptoms do not resolve after high-dose corticosteroid pulse therapy [MSTCG, 2004]. In some patients with severe symptoms at onset, which do not respond to steroids, plasma exchange therapy may be considered as escalating relapse therapy [Keegan *et al.* 2002]. The goal of corticosteroids and/or plasma exchange is to optimize recovery from a severe relapse in the short term (i.e. long-term benefit in modifying the disease course is not a goal). In contrast, the primary goal of DMT is to prevent

future disabling relapses and hopefully slow or prevent progression.

Recently, concepts of escalation and induction immunotherapy in MS have been proposed [Martinelli and Comi, 2005; Edan *et al.* 1997]. Induction therapy mainly focuses on patients with severe onset with multiple relapses, and it encompasses short-lasting intensive immunosuppression followed by maintenance treatment with an immunomodulatory disease-modifying agent (DMA) once clinical stability has been obtained. Escalating immunotherapy represents a therapeutic strategy based on a reasonable decision-making procedure in which drugs with the best risk/benefit ratio are first preferred and, if needed, drugs with increasing power and/or toxicity (but not necessarily more efficacy) are successively adopted. Both strategies may be valuable options for patients starting on DMT; however, starting treatment after the first attack will more likely apply to the concept of escalating immunotherapy if first-line treatment fails (Figure 1).

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Figure 1. The challenge of immunomodulatory treatment. Finding the most effective treatment for an individual patient.

Various challenges exist for early DMT (Box 1). Patients eligible for early DMT should be provided with simple and clearly understandable information regarding realistic therapeutic goals, as well as an explanation of the mechanisms of action and possible adverse effects of therapies in order to allow for an informed decision process [Heesen *et al.* 2004].

The decision to start immunotherapy after CIS has major implications for follow-up, as criteria for response to treatment based on a reduction in relapses cannot be assessed for individuals with a history of only one prior event. Therefore, it is recommended to define thresholds with the patient at the time of initiating DMT, which will trigger further investigations to assess disease stability during therapy and also establish the concept for escalating therapy. The following dimensions of disease activity should guide this process: quality of life, frequency, severity and resolution of relapses, cognitive changes, disability progression and subclinical disease activity on MRI. Although validation of these parameters in the early phase of MS has not completely been achieved they may be used as relevant areas for patients' or physicians' concerns. Patients may need to be provided with a working definition for relapses to aid in distinguishing new disease activity from residual symptoms that can fluctuate on a daily basis. Thresholds for these outcomes have been defined using the three-gauge model [Freedman *et al.* 2004; MSTCG, 2004] with categories of 'low', 'medium' and 'high risk' for treatment failure, but this model has not yet been validated in the long-term use with real data.

To monitor the efficacy of immunotherapy and improve compliance, follow-up clinical evaluations

Box 1. Challenges of early disease modifying treatment.

- Correct diagnosis by applying the complete McDonald criteria
- Consequent treatment of initial relapse symptoms
- Select the right patients with clinically isolated syndromes for early disease-modifying treatment based on disease activity and severity of initial symptoms (e.g., polysymptomatic onset)
- Define realistic treatment goals with the patient
- Set thresholds for alert of suboptimal treatment response
- Discuss the concept and limitations of escalating immunotherapy (class III evidence) with the patient.

should be carried out at three-monthly intervals during the first year of treatment utilizing standard MS scales, such as the expanded disability social scale (EDSS) or the multiple sclerosis functional composite (MSFC) scale. Special attention should be paid to side-effects of injectable treatments and hidden symptoms, such as depression or urinary tract infection, as they may mimic treatment failure. Frequent clinic/office visits during the first year of treatment are therefore important in order to achieve an optimal tolerance of, and adherence to, treatment to establish a confident patient/physician relationship and receive continuous feedback on the patient's clinical activity during the important early years of disease evolution [Rio *et al.* 2005]. Using this approach, it is the main goal to maintain disease stability related to the dimensions of quality of life, relapse frequency and intensity, as well as cognitive performance and physical activity (Figure 2).

Supporting evidence for these recommendations come both from analysis of phase III studies of drugs approved for basic therapies and cohort studies from large MS centers. For example, patients with ongoing relapse activity during basic therapy are more likely to progress on their EDSS in short-term follow-up after 2–3 years. This was also seen in patients with high numbers of new lesions on serial MRI [Farina *et al.* 2005; Rudick *et al.* 2004]. However, early disability progression during initial DMT was demonstrated to have the highest sensitivity, specificity and accuracy to predict disability outcome after 6 years [Rio *et al.* 2006].

Consensus criteria to define treatment failure were developed among US MS centers and included relapse rates of either one per year or

Figure 2. Standardized algorithm to follow relapsing/remitting multiple sclerosis patients during immunotherapy [modified after MSTCG 2004]. EDSS, expanded disability social scale; MSFC, multiple sclerosis functional composite.

unchanged from pretreatment rates, incomplete recovery from multiple attacks, evolution of polyregional neurologic involvement, recurrent brainstem or spinal cord lesions, and cumulative loss of neurologic function sufficient to disrupt daily activities [Cohen *et al.* 2004].

The clinical and radiologic impact of developing neutralizing antibodies (NABs) to interferon-beta (IFN- β) while on this MS therapy is another important area to define response to treatment. There is now overall agreement that treatment with IFN- β (Avonex, Betaseron/Betaferon or Rebif) is associated with the production of NABs and that IFN- β -1a (as it is currently formulated for i.m. injection) is less immunogenic than the other IFN- β preparations (either IFN- β -1a or IFN- β -1b) given multiple times per week subcutaneously. As there are still differences in NAB test sensitivity and quality there is no consensus on when to test, which test to use, how many tests are necessary, or which cut-off titer to apply for determination of nonresponders.

Very specific and far-reaching recommendations were provided by the taskforce of the European Federation of Neurological Societies. They concluded that tests for the presence of NABs should be performed in all patients at 12 and 24 months of treatment and therapy with IFN- β should be discontinued in patients with high titres of NABs sustained at repeated measurements with

3–6 month intervals [Sorensen *et al.* 2005]. At the other end of the spectrum, the therapeutics and technology assessment subcommittee of the American Academy of Neurology concluded in their recommendations that there is still insufficient information on the utilization of NAB testing to provide clinical guidance about whether or not to stop IFN- β treatment only on the presence of a positive test, which has not been thoroughly evaluated in inter-laboratory comparisons [Goodin *et al.* 2007]. This more conservative view is shared by the multinational MS therapy consensus group, representing members of the medical advisory boards to their national MS societies [MSTCG, 2008] and the Canadian Network of MS Clinics [O'Connor and Devonshire, 2008]. As there are currently different tests and standards for NAB measurements being used, there is now an effort to use a single unit to measure NABs – the TRU (Tentime Reduction Unit), after S. Grossberg [Grossberg *et al.* 2001]. Further, they are comparing the use of different assays to measure NABs. In our hands, it is evident that NABs do not affect the three available products to the same extent [Boz *et al.* 2007].

Cognitive performance and quality of life during basic therapy are rated as important dimensions among patients to determine optimal treatment response [Rothwell *et al.* 1997]. Unfortunately, this important area is still under-represented in

publications related to treatment response, but there is evidence that basic DMTs have a positive therapeutic effect on cognitive dysfunction, unrelated to their effects on the EDSS score and course of the disease [Flechter *et al.* 2007; Pierson and Griffith, 2006].

Therefore, an integrated two-step approach to determine treatment failure as recently outlined by the MSTCG [Rieckmann *et al.* 2004] is recommended, as follows:

1. Define 'red flags' in the domains of quality of life, cognitive performance and relapse activity reported by the patient during clinic visits and verify changes in clinical status by quantitative neurologic examinations using established scores, like the EDSS and MSFC. If alert thresholds are met and further evidence is needed, order objective paraclinical examinations.
2. Obtain a brain MRI using a standardized protocol for comparison [Simon *et al.* 2006], to scans performed before initiation of DMT, and order NAB test if patients are currently on IFN- β treatment.

Based on the results of these examinations and using the three-gauge model with individually predetermined thresholds, a shared informed decision to continue or stop the ongoing DMT can be made.

What to choose next, if first-line DMT fails?

There is currently no class I evidence study to support the use of escalating immunotherapy in suboptimal treatment responders; thus, we have to consider that any decision made at this stage of the therapeutic algorithm is based on less solid evidence than at the start of treatment. With these limitations in mind, an individual approach to choosing the optimal strategy should be based on the age-at-onset and the degree of disease activity during basic therapy, as well as a consideration of the different modes of drug action. Possible options are presented in Box 2. Primary nonresponders to treatment may be switched to another modality of basic treatment, as different pathogenetic mechanisms may operate. A recent prospective observational study demonstrated that 56–81% of patients were relapse-free at 3 years after switching from either glatiramer acetate to IFN- β or vice versa due to a suboptimal response to the initial treatment [Carra *et al.* 2008].

Box 2. Possible options for multiple sclerosis patients with suboptimal response to first-line disease-modifying therapy.

- Exclude other reasons (e.g. hidden symptoms such as depression or infections)
- Improve symptomatic treatment including reduction of side effects.
- Change to high-dose, high-frequency IFN- β in patients on i.m. IFN- β -1a who are negative for neutralizing antibodies (NAB)
- Switch to glatiramer acetate in patients with persistent NAB on IFN- β therapy
- Switch to IFN- β if suboptimal response to treatment with glatiramer acetate
- Switch to natalizumab in patients with ongoing disease activity during basic therapy
- Add repeated corticosteroid pulses at monthly intervals for a limited period
- Combine basic therapy with immunosuppressant drugs, such as methotrexate or azathioprine.
- Escalate to cytotoxic drugs, such as mitoxantrone or cyclophosphamide, if rapid disease progression during basic therapy.

In patients with breakthrough disease after initial stabilization (secondary nonresponder), repetitive high-dose corticosteroid pulses at monthly intervals have been suggested as an initial option to prevent accumulating deficits [Boster *et al.* 2008; Rieckmann *et al.* 2004; Stuart, 2004]. Another option to improve response to basic therapy is the combination with another basic DMT. This approach has been thoroughly evaluated in other autoimmune diseases such as rheumatoid arthritis [Donahue *et al.* 2008] but efficacy data to support such an approach to optimize MS treatment are still very limited and do not reach class I evidence [Gold, 2008; Fernandez, 2007]. There is one single exception of a highly effective combination therapy in a phase III trial with class I evidence; however, the SENTINEL study (IFN- β -1a plus natalizumab) [Rudick *et al.* 2006], resulted in two cases of severe progressive multifocal leukoencephalopathy (PML, one death) and was therefore not approved by the FDA (see below).

Combinations trials of immunosuppressants (azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil, mitoxantrone and statins) with IFN- β have mainly focused on early side-effects and tolerability, which were generally reported to be good. However, all of these trials included only small numbers of patients, which precludes any statement on potential efficacy

of this approach in nonresponders to monotherapy [Fernandez, 2007].

Studies to optimize treatment strategies with glatiramer acetate include a recently completed induction trial with mitoxantrone, followed by glatiramer acetate [Vollmer *et al.* 2008; Ramtahal *et al.* 2006]. Again, the authors demonstrated a reasonably good side-effect profile but efficacy results were limited due to missing control groups. There is a large ongoing NIH-funded phase III study to evaluate the efficacy of the combination of IFN- β -1a and glatiramer acetate in treatment-naïve patients with relapsing/remitting MS (RRMS), but this strategy has not been evaluated in suboptimal treatment response during monotherapy. Overall, the above-mentioned approaches to combination or add-on therapy for patients with suboptimal response to monotherapy are encouraging but no convincing evidence has yet emerged due to lack of large, controlled and randomized phase III trials.

Intensive immunosuppression for nonresponders

For patients with frequent relapses and continuous clinical worsening despite first or second-line immunomodulatory treatment (IFN- β , glatiramer acetate) and repeated corticosteroid pulses, intensive immunosuppression with cyclophosphamide, mitoxantrone or even autologous bone marrow stem transplantation may be considered as an immediate treatment option. In this situation of escalating immunotherapy, the current drug will be stopped and immunosuppression will be initiated following careful examination of potential exclusion criteria and comprehensive re-evaluation of the overall disease activity, including brain MRI and evoked potentials, in order to define a new baseline, which will allow evaluation of the response to the new treatment (Figure 2) [Rieckmann *et al.* 2004].

Mitoxantrone

This cytotoxic drug was developed to treat malignancies. It inhibits topoisomerase II, thereby delaying cell-cycle progression of rapidly dividing cells. Immunologically, it has a major effect on B-cell function and also induces apoptosis of lymphocytes [Chan *et al.* 2005]. The drug has a long half-life of 9 days and was first used in progressive multiple sclerosis in the early 1990s. The first placebo-controlled trial of mitoxantrone was

published by Millefiorini and co-workers in 1997. Monthly infusions of mitoxantrone (8 mg/m² for 1 year) were compared with saline infusions in patients with RRMS. A significant reduction in the annual relapse rate and an increase in the number of relapse-free patients at year 1 and 2 in the mitoxantrone-treated group, but no difference in mean EDSS was observed [Millefiorini *et al.* 1997]. A larger phase III trial with 194 patients of worsening RRMS or secondary progressive MS was presented by Hartung and colleagues and led to the approval of mitoxantrone as the first escalating immunotherapy in MS [Hartung *et al.* 2002]. In this multicenter study, patients were either randomized to receive placebo or mitoxantrone (12 mg/m² or 5 mg/m²) every 3 months for a period of 2 years. The higher dose of mitoxantrone revealed a significantly larger effect on the combined primary endpoint (change from baseline EDSS at 24 months, change from baseline in ambulation index at 24 months, number of treated relapses, time to first treated relapse and change from baseline-standardized neurological status at 24 months). In this trial, the higher dose did not reduce the number of MRI scans with positive gadolinium (Gd) enhancement at months 12 and 24 *vs* placebo. Results of secondary MRI outcome measures suggested a positive impact of both mitoxantrone doses on some of the Gd enhanced and unenhanced MRI measures [Krapf *et al.* 2005], which was already seen in the initial trial with mitoxantrone [Edan *et al.* 1997].

A recently published observational study reported the effects of an induction therapy with monthly doses of mitoxantrone (20 mg i.v.) in combination with prednisone (1000 mg i.v.) over a period of 6 months followed by de-escalating immunotherapy with a mean follow-up period of 3.8 years [Le Page *et al.* 2008]. In patients that were continued on either mitoxantrone every 3 months, IFN- β , glatiramer acetate, azathioprine or methotrexate, a significant reduction of relapse rate, EDSS score and MRI activity was observed from year 1 up to 5 years after induction therapy. In a retrospective analysis of patients, who failed immunotherapy with azathioprine, IFN- β -1b or cyclophosphamide, Cursiefen and co-workers reported a sustained effect on relapse rate reduction and disease progression in 15 patients treated for at least one year with mitoxantrone (10 mg/m² every 3 months) [Cursiefen *et al.* 2000].

One small open-label, prospective add-on study in ten patients with suboptimal treatment response to at least 6 months therapy with IFN- β -1b reported a reduction in MRI disease activity by 96% and relapse rate by 64%, if mitoxantrone (12 mg/m^2) was used at month 1, followed by 5 mg/m^2 at month 2 and 3 and continued at three-monthly intervals [Jeffery *et al.* 2005]. Based on the above-mentioned data, mitoxantrone was recommended as a second-line drug by several consensus initiatives for patients with worsening MS and a suboptimal response to basic DMT [O'Connor and Devonshire, 2008; Cohen *et al.* 2004; Rieckmann *et al.* 2004].

Cyclophosphamide

This alkylating drug interferes with cell replication and causes long-lasting suppression of cell-mediated and humoral immune responses. It was initially established as one of the first successful immunosuppressants in devastating vasculitis (e.g. Wegener granulomatosis) [Fauci *et al.* 1971]. The first study in MS was published in the mid-1970s [Hommes, 1978]. Eighty-six patients with chronic progressive MS were treated with a short course of cyclophosphamide (400 mg) plus prednisone (1 g) per day in an uncontrolled, open-labeled fashion. With this regimen, stabilization of disease was obtained in 69% of patients for 1–5 years. Controversies about the effectiveness of cyclophosphamide arose after conflicting results were published from two North American trials in the 1990s. A four-arm study, which randomized 256 patients with progressive MS to either i.v. cyclophosphamide and ACTH, with or without i.v. boosters every other month; or i.v. cyclophosphamide and ACTH, given at a modified induction regimen (cyclophosphamide 600 mg/m^2 i.v. on day 1, 2, 4, 6 and 8) with or without i.v. boosters [Weiner *et al.* 1993]. Patients receiving i.v. boosters had a significant delay in reaching time-to-treatment failure as defined by a one-point increase in EDSS confirmed after 2 months. A treatment-greater effect was also observed in patients under the age of 40.

In the second, single-blinded trial, 168 patients with progressive MS were randomized to either i.v. cyclophosphamide with oral prednisone, oral cyclophosphamide and oral prednisone on alternate days with weekly plasma exchange or oral placebo and sham exchange. No significant differences between the treatment groups were detected for the prespecified endpoint of EDSS

worsening (≥ 1 EDSS point confirmed after 6 months) [Canadian Cooperative Multiple Sclerosis Study Group, 1991]. More recent studies described positive effects of different dose regimens for cyclophosphamide in patients failing basic immunotherapy. Hohol and colleagues demonstrated a beneficial effect of a monthly combination of i.v. cyclophosphamide with prednisone pulses in 95 patients with progressive MS. Eighty percent of these patients had a stable or improved EDSS after 12 months of treatment [Hohol *et al.* 1999]. Khan and coworkers treated 14 consecutive RRMS patients with monthly cyclophosphamide infusions, who had rapidly deteriorated while on basic immunomodulatory treatment [Khan *et al.* 2001], which resulted in stable EDSS and relapse free periods up to 18 months follow-up.

A retrospective analysis of 490 patients with SPMS or PPMS who were treated with monthly pulses of i.v. cyclophosphamide over a period of 12 months demonstrated stable or improved EDSS values compared to baseline in two-thirds of all patients. A shorter disease duration was of prognostic value for a response to treatment [Zephir *et al.* 2004].

In one multicenter trial, 59 patients who did not respond to IFN- β , were randomized to either receive monthly add-on i.v. cyclophosphamide infusions or monthly corticosteroid pulse therapy. Significantly reduced disease activity as measured by relapse frequency and Gd-enhancing lesions on MRI was reported in the cyclophosphamide group [Smith *et al.* 2005].

Although most data from the above studies point to a positive treatment effect of cyclophosphamide in patients with RRMS or SPMS and insufficient response to initial basic DMT, the optimal time to initiate treatment, duration and drug regimen are still to be determined in a prospective controlled trial with proper inclusion criteria of nonresponders.

Autologous bone marrow transplantation

The rationale behind this very intense method of immunosuppression is, in simple words, 'to replace the immune system and eradicate auto-immune cells'. There are three steps in the bone marrow transplantation:

1. mobilization and collection of hematopoietic stem cells via leukapheresis

2. complete ablation of the immune system by high dose cytotoxic drugs
3. reinfusion of the stem cell graft.

It is hoped that this procedure will exclude all autoimmune components by reinfusion of the stem cell graft to induce better tolerance to self-antigens and thereby reduce the risk of further autoimmune attack. However, it is still not clear whether all immune cells behind the blood–brain barrier, within the lesions and particularly long-living antibody-producing plasma cells can be destroyed by this approach [Tyndall *et al.* 2007]. The mortality rate for this procedure in the autologous setting is still between 5% and 10%.

The procedure has mainly been applied to MS patients with a rapidly progressive disease course – either RRMS or SPMS – after other DMTs have failed. Reported studies are rather small and different protocols were used, which makes it difficult to compare across the different approaches. In one study, 24 MS patients were followed for up to 40 months after transplantation, and improvement or stabilization in 18/24 patients and one death was observed. Ninety-two percent of patients with SPMS were progression-free at year 3 of follow-up [Fassas and Kimiskidis, 2003]. In a multicenter study performed by Nash and coworkers, 26 patients with different forms of MS were treated with immunoablative therapy followed by autologous stem cells, and disease stability was achieved in 91% at year 3. In another small study, the 3-year progression-free probability was 85.7% and brain MRI active lesions were completely resolved [Saiz *et al.* 2004].

Changes in brain volume (decrease by 3.2% over a median time of 2.4 months) were recently described, which were higher than expected from the resolution of edema and T2-lesion reduction [Chen *et al.* 2006]. Interestingly, in the Canadian bone marrow stem cell trial significant changes in the magnetization transfer ratio, consistent with remyelination in acute lesions, was detected on serial scans [Chen *et al.* 2008].

Overall, autologous stem cell transplantation is still a highly experimental procedure, with many open questions related to patient selection, toxicity and treatment-related brain atrophy. Therefore, this procedure should only be applied to patients in a clinical trial setting performed in specialized centers [Boster *et al.* 2008; Rieckmann *et al.* 2004].

New developments

Natalizumab

This monoclonal antibody against $\alpha 4$ -integrin reduces immune-cell traffic across the blood–brain barrier and was tested in two large, multicenter trials in RRMS. In the phase III AFFIRM study, monotherapy with natalizumab resulted in a 68% reduction in relapse rate, 42% reduction in disease progression and 92% reduction of active, Gd-enhancing MRI lesions compared with placebo [Polman *et al.* 2006]. In the second trial (SENTINEL study) natalizumab was added to i.m. IFN- β -1a in patients who still had ongoing disease activity while on IFN- β -1a therapy. Compared with patients, continued on IFN- β -1a monotherapy, the combination of both drugs resulted in a 24% reduction in the relative risk of sustained disability progression. Combination therapy was also associated with a lower annualized rate of relapse over a two-year period than was IFN- β -1a alone and with fewer new or enlarging lesions on T2-weighted MRI [Rudick *et al.* 2006].

The impressive reduction in relapses in the AFFIRM trial led to an accelerated approval of the drug by the FDA but this was temporarily suspended after two cases of PML were diagnosed in MS patients who received the combination therapy in the SENTINEL study. After careful analysis of all reported side-effects during trials with natalizumab (there was another case of fatal PML in a patient with Crohn's disease), natalizumab was subsequently reapproved only as a second-line monotherapy for relapsing forms of MS in patients who have not responded to immunomodulatory basic therapy. Note that a report of two European cases of PML with natalizumab monotherapy were presented by Prof. Ralf Gold (Bochum, Germany) in August 2008 at this year's EFNS meeting in Madrid. This is discussed in more detail in the editorials in this issue of the journal [Phillips and Frohman, 2008; Racke and Stüve, 2008].

Besides the risk for PML, which is currently estimated at 1:1000, other opportunistic infections must be considered and careful patient selection requires pretreatment brain MRI, use of natalizumab only as monotherapy after appropriate washout periods of other immunomodulators and education about the risk for, and symptoms of, PML [Kappos *et al.* 2007]. Recommendations for use of natalizumab have been provided by different groups, and recent data from postmarketing surveillance programs

(TOUCH and TYGRIS) did only reveal two further cases of PML in over 30,000 treated patients so far. This places natalizumab at a more favourable benefit to risk ratio than mitoxantrone or other immunosuppressive strategies. Based on the available evidence, the use of natalizumab is therefore recommended in patients with suboptimal response to basic therapy with beta-interferons. Discontinuation of immunomodulatory agents for at least 1 month and at least 6 months for immunosuppressants before starting natalizumab is recommended [Boster *et al.* 2008; MSTCG, 2008].

Further options for escalating immunotherapy

Currently several new promising pharmaceutical compounds are being tested in phase II and phase III trials to reduce disease activity in RRMS. These drugs include oral medications [Cohen and Rieckmann, 2007] and biologicals including monoclonal antibodies [Buttmann and Rieckmann, 2008]. Examples include teriflunomide [O'Connor *et al.* 2006], fingolimod (FTY 720) [Kappos *et al.* 2006], laquinimod, BG-12 [Kieseier and Wiendl, 2007] and cladribine [Sipe, 2005]. 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 II trials [Hauser *et al.* 2008; Jones and Coles, 2008; Schrijver *et al.* 2008; Rose *et al.* 2007]. Further phase II and III trials with these agents are ongoing. 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. However, it is not currently recommended outside of clearly defined approved research protocols. Alemtuzumab seems to have high anti-inflammatory potential as it was superior to high-dose Rebif in a direct, though unblinded, head-to-head trial. However it has the potential risk of opportunistic infections and other autoimmune disorders (thyroid autoimmunity, idiopathic thrombocytopenic purpura) occurred during therapy. Rituximab is an interesting alternative as a B-lymphocyte depleting agent [Bar-Or *et al.* 2008] and may have potential in patients who do not respond to more T-cell directed therapies (e.g. IFN- β and glatiramer acetate). Evidence about the important role of B cells in the pathogenesis of MS is accumulating [McFarland, 2008], and we can anticipate that other strategies interfering with B-cell activation may soon appear on the scene of new MS therapies. The occurrence of PML has also been described with relation to rituximab therapy in patients with systemic lupus erythematosus and thus stresses the importance of not using this drug off-label outside proper clinical trials.

With the advent of these different new promising therapies, we have to wait until phase III data are available and approved for the specific indication. It is evident that more effective drugs may also carry a higher risk for severe side-effects; indeed, some of them may pose a greater threat to patients than MS itself. Therefore, once the new drugs become available, we have to be prepared for a thorough risk/benefit analysis in view of all the different immunotherapeutic strategies available (Figure 3).

Figure 3. Risk/benefit ratio for escalating immunotherapy in relapsing/remitting multiple sclerosis. Note that after basic disease-modifying therapy (interferons and glatiramer acetate), the only drug with clear efficacy is natalizumab. Mitoxantrone and cyclophosphamide are second-line options for treatment failure, and bone marrow transplantation or combination therapy are third-line options (no/limited evidence of efficacy).

How to overcome the lack of evidence

With the worldwide increase in numbers of patients treated with basic immunomodulatory therapies, which are only partially effective, we may soon face a scenario where patients who are either suboptimal responders or have intolerable side-effects will be switched to other treatments either within the established primary DMT or escalated to receive natalizumab, mitoxantrone or cyclophosphamide without proper evidence from clinical trials. This situation is of course very unfortunate, as ongoing disease activity during DMT increases the risk for permanent disability. MS patients require evidence-based advice and choice of therapy must be based on an informed decision about the risk/benefit ratios of the different therapies available for escalating immunotherapy [MSTCG, 2008].

In other autoimmune disease such as rheumatoid arthritis, combination therapies and treatment escalation are much better evaluated and evidence-based decisions can be derived from study data – which included patients not responding well to basic therapy with established drugs (e.g. steroids or methotrexate) [Donahue *et al.* 2008; Smolen *et al.* 2007]. Therefore, we argue for an urgent call to establish randomized controlled clinical trials that also includes patients who have failed on basic therapy. These trials face the challenge of selecting an appropriate control group (as placebo is not an option in advanced disease) and performing proper sample size collection based on current use of escalating DMTs.

Pre- versus post-intervention analysis of relapse rates and disease progression (or number of patients progressing), and disease-activity-free patients can be used as exploratory endpoints in phase II settings, but head-to-head comparisons of two escalating strategies in a parallel-group design is the gold standard we should aim for. In order to achieve this, MS specialists will have to approach the pharmaceutical industry and national funding agencies with new proposals for design of class I evidence studies to evaluate the concept of escalating therapy in the setting of investigator initiated trials.

Conflict of interest statement

None declared.

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