Multiple Sclerosis Therapy
Consensus Group

Escalating immunotherapy
of multiple sclerosis
New aspects and practical application

Abstract Recent clinical studies in multiple sclerosis (MS) provide new data on the treatment of clinically isolated syndromes, on secondary progression, on direct comparison of immunomodulatory treatments and on dosing issues. All these studies have important implications for the optimized care of MS patients. The multiple sclerosis therapy consensus group (MSTCG) critically evaluated the available data and provides recommendations for the application of immunoprophylactic therapies.

Initiation of treatment after the first relapse may be indicated if there is clear evidence on MRI for subclinical dissemination of disease. Recent trials show that the efficacy of interferon beta treatment is more likely if patients in the secondary progressive phase of the disease still have superimposed bouts or other indicators of inflammatory disease activity than without having them. There are now data available, which suggest a possible dose-effect relation for recombinant beta-interferons. These studies have to be interpreted with caution, as some potentially important issues in the design of these studies (e.g. maintenance of blinding in the clinical part of the study) were not adequately addressed. A meta-analysis of selected interferon trials has been published challenging the value of recombinant IFN beta in MS. The pitfalls of that report are discussed in the present review as are other issues relevant to treatment including the new definition of MS, the problem of treatment failure and the impact of cost-effectiveness analyses. The MSTCG panel recommends that the new diagnostic criteria proposed by McDonald et al. should be applied if immunoprophylactic treatment is being considered. The use of standardized clinical documentation is now generally proposed to facilitate the systematic evaluation of individual patients over time and to allow retrospective evaluations in different patient cohorts. This in turn may help in formulating recommendations for the application of innovative products to patients and to health care providers. Moreover, in long-term treated patients, secondary treatment failure should be identified by pre-planned follow-up examinations, and other treatment options should then be considered.

Key words multiple sclerosis · immunotherapy · consensus

Introduction

In 1998, members of the medical advisory boards from 3 European MS societies (Austria, Germany and Switzerland) met for the first time to develop evidence-based treatment recommendations for immunomodulatory therapy of multiple sclerosis wherever these are available. It was also planned to consider treatments where the criteria of evidence-based recommendations are not yet met. The first manuscript was published in 1999 [32] followed by an English version soon thereafter [43]. A consensus on treatment recommendations was reached after systematic review of published study data according to a stringent classification of evidence [20, 42].

The experience of the last few years in the three countries of the original MSTCG initiative (Austria, Ger-
many, Switzerland) demonstrates that the evidence-based consensus recommendations have indeed contributed to improve the care of MS patients in various ways. In June 2002, at a meeting of the European multiple sclerosis platform, several MS societies expressed their desire to participate in the MSTCG. Therefore, a new English version was written and distributed to European MS societies. Comments and suggestions were incorporated and finally the updated version was approved by all co-authors. MSTCG can now be regarded as a multi-national task force to improve immunomodulatory treatment options for MS patients in Europe.

In this version we have extended our review to additional practical aspects that are closely linked to treatment issues. The following topics will be addressed:

### New diagnostic criteria for multiple sclerosis

The diagnostic criteria for MS formulated by Poser [40] date back to the time, when magnetic resonance imaging (MRI) had just arrived on the scene with regard to MS diagnosis. The predictive value of this new technique for the course of the disease could not be estimated at that time. Several longitudinal studies on the natural course of the disease drew considerable attention to the role of lesion load on MRI at the time of the first isolated clinical symptom [1, 38, 51]. It was shown that patients with lesions on initial MRI have an increased risk for a second relapse and development of clinically definite multiple sclerosis within the next two years. Early lesion load also implies a higher risk of progressive disease after two, five and ten years. Furthermore, it is now accepted that the true onset of the disease may be long before the first clinical symptoms become evident. This is also reflected by asymptomatic abnormalities on evoked potentials already present at the first clinical episode. Finally, new sophisticated MRI techniques, such as magnetisation transfer ratio (MTR), magnetic resonance spectroscopy (MRS), and measures of atrophy indicate that axonal damage and loss of brain volume can be detected already at early stages of the disease [3, 12]. In view of these findings, any disease modifying treatments should start at an early time point in order to halt or slow down disease progression. Indeed, these therapeutic implications are supported by clinical studies (CHAMPS and ETOMS) [7, 9, 22]. Therefore the established diagnostic criteria were revised and updated by an international expert panel to now include “evidence of subclinical disease activity” as seen on MRI, into the MS-defining criteria as an important indicator for dissemination in time and space [30]. These new diagnostic criteria were recently validated in two prospectively planned studies [10, 52] and appear to be more sensitive in predicting future relapse and MRI activity than the Poser criteria [40].

Using the McDonald criteria, the presence of subclinical disease activity (new T2 lesions or Gd+ lesions in defined locations) on MRI more than 3 months after the first clinical presentation can substitute for a second relapse. In practical terms, MS can now be diagnosed already 3 months after a first clinical episode [30]. Consequently, earlier immunomodulatory therapy is now possible because the diagnosis of active MS can be established at a much earlier time point using MRI as a surrogate for disease dissemination. In this new setting, it is imperative that diseases other than MS (e.g. cerebral vasculitis or neuro-borreliosis) are excluded by appropriate ancillary tests – in particular CSF analysis [40] – before accepting the diagnosis MS and starting treatment. According to the new criteria, MS is now classified as “definite” – “possible” – or “no MS”.

### Initiation and duration of immunomodulatory treatment

#### Indication for basic therapy

According to our previous recommendation immunomodulatory therapy was felt to be indicated in cases of an ‘active course of the disease with at least two functionally relevant bouts within the last two years or the appearance of one severe attack with reduced recovery’ [43].

Apart from this statement issued by the MSTCG, recommendations for the application of immunoprophylactic therapies were independently provided by the National Multiple Sclerosis Society of the United States [33] and the Canadian Multiple Sclerosis Clinical Network [36]. There is now consensus among these expert panels that therapy should be started ‘as soon as possible’, but no clear definition of a time frame was provided.

#### Studies on early treatment with recombinant interferon β (CHAMPS and ETOMS)

There are two published studies on early immunomodulatory therapy in multiple sclerosis [7, 22]. Both trials (CHAMPS, sponsor: BIOGEN; ETOMS, sponsor: SERONO) recruited patients after the first clinical attack upon proof of disseminated lesions on brain MRI in a MS-typical distribution. Both studies were randomised, placebo-controlled multi-center trials using recombinant interferon β–1a once weekly (CHAMPS: Avonex 30 μg i. m.; ETOMS: Rebif 22 μg s. c.). The time from the presentation of first clinical symptoms to inclusion into the study was less than 28 days in the CHAMPS study and less than 3 months in the ETOMS study. The CHAMPS protocol included compulsory high-dose cor-