

Chapter 20. Multiple Sclerosis and Other Demyelinating Diseases

Giancarlo Comi, M.D.¹

Michel Clanet, M.D.²

Fred Lublin, M.D.³

Vittorio Martinelli, M.D.⁴

Chris H. Polman, M.D.⁵

Per Solberg Sorensen, M.D.²

¹ Department of Neurology
University Vita-Salute IRCCS San Raffaele
Via Olgettina, 60
20132 Milan
ITALY
Tel +39/02/26432990
Fax +39/02/26433746
Email comi.giancarlo@hsr.it

² Department of Neurology
Hospital Purpan
Toulouse
FRANCE

³ Department of Neurology
VU Medical Centre
Amsterdam
THE NETHERLANDS

⁴ Department of Neurology
University Vita-Salute IRCCS
San Raffaele, Milan
ITALY

⁵ Department of Neurology
Copenhagen University Hospital
DENMARK

Corresponding Author:
Giancarlo Comi, M.D.

I. INTRODUCTORY REMARKS

Multiple Sclerosis (MS) is a devastating disease affecting predominantly the white matter of the central nervous system. It is the most frequent cause of disability in young adults, after car accidents. The disease affects about one million people, mostly in developed countries. In fact the disease has a peculiar geographic distribution, probably as a result of an interaction of genetic and environmental factors, being more frequent in North America and North Europe and almost absent in equatorial regions and in Asia. Environmental factors are completely unknown and genetic factors have been only partially revealed, with a key role for genes involved in regulatory mechanisms of the immune system. No preventing strategies are available.

In 1993 FDI approved the use of Interferon Beta 1b for the treatment of relapsing remitting MS. Shortly later both Interferon beta 1a and Interferon beta 1b were approved by drug agencies worldwide and Glatiramer Acetate was approved in the end of the nineties. Finally Interferon beta 1b was approved also for treatment of secondary progressive multiple sclerosis. Soon after the approval of these immunomodulating agents, new phase II-III clinical trials were started to explore the best dose and frequency of injection for available therapies, to evaluate combination treatments and to tests safety and efficacy of new treatments. Immunosuppressive agents have been extensively used to treat MS since more than thirty years, however only recently mitoxantrone has been approved by FDI for treatment of active MS patients not responding to immunomodulating agents.

There are converging and convincing evidences that early treatment is more effective in MS and that both Interferons (IFNs) and Glatiramer Aceate (GA) produce little or no benefits in the progressive phases of the disease. Multi-weekly injections, particularly in the initial period of treatment, resulted superior to the weekly injection. However increasing dose and frequency of injection result in a higher frequency of anti-interferon antibodies, which, if persistently present may limit the efficacy of treatment.

New therapies have a broad range of targets, including the T cell receptor, the co-stimulation molecules, the blood-brain barrier permeability, chemokines, etc. It has been estimated that about one hundred clinical trials are ongoing in Europe and North America. Most of these trials have a placebo control group, which raises ethical and practical issues because of the availability of active treatments. Ethical concerns for placebo arm are particularly relevant for phase III clinical trials because the study duration is usually not shorter than 2 years.

Combination therapy, an approach derived by treatment of tumours, is already in use in some MS centres, however the efficacy of this therapeutic strategy has not been proved yet. Two approaches are generally used: 1) the comparison between treatment A and the combined treatment A+B (where treatment A is Glatiramer Acetate or Interferon beta 1b); 2) treatment A is compared to treatment B followed by treatment A (where treatment B is usually an immunosuppressive agent).

MS is not a homogenous disease. Three main courses have been described, relapsing-remitting (RR), secondary progressive and primary progressive, to which we should add atypical variants such as Marburg's disease, Devic's disease and Balo's disease. Post mortem and biopsy studies revealed that MS subtypes are characterised by different pathological findings and that in the same patient pathogenetic mechanisms may vary along the disease course. This intra- and inter-individual variability of the dysfunction of the immune system may be one of the reasons why the response to immunomodulators is so variable in MS patients. It is possible that future trials will concentrate on a more homogenous group of patients using a combination of clinical, instrumental and genetic parameters.

The efficacy of IFNs and GA on MS disease activity, at least in patients with RR disease is definitely proved. However, also in this population of patients, it is still debated if the "anti-inflammatory" activity of IFNs and GA also produce long term effects on disability. There are some contradictions among

clinical trials performed in RRMS on the effects on disability, explained by methodological problems (problems in the definition of progression, sample size, study duration, poor responsiveness of EDSS etc.) and by differences in the included population. Long term placebo controlled studies in RRMS, so necessary to prove trial benefits for the prevention of the accumulation of irreversible nervous damage, are not possible anymore for ethical and practical reasons. On the other hand, comparison with epidemiological data are very difficult to interpret. The open or blind extension of placebo controlled clinical trials with the comparison of patients with early and delayed active treatment may give problems of interpretation of the results because of the patients lost to the follow up and the frequency of patients switched to other treatments.

In Secondary Progressive MS all clinical trials failed to show efficacy and only the European Multicenter trial was able to demonstrate a significant effect of IFN beta1b on the proportion of patients with confirmed increase of EDSS score. No significant effects on disability were observed in clinical trials evaluating the effects of IFNs and GA in Primary Progressive MS.

The problem of paraclinical endpoints has been widely discussed in many meetings. Their use for phase II clinical trials in RR patients, has been accepted by national and supranational drug agencies because active MRI lesions are a more precise and sensitive measure of disease activity than the count of the number of relapses. In phase III trials in RRMS and in progressive MS courses only disability measures are accepted as primary endpoint; MRI surrogate markers may be used only as secondary or exploratory measures.

II. PHASE II STUDIES FOR REGISTRATION OF NEW DRUGS

Phase II studies in MS have been mostly short term, i.e., approximately six months and designed to answer two main questions: 1) proof of principle of the proposed agent and 2) dosing information. Safety monitoring, as always, is also a prime consideration. To date, most phase II MS clinical trials have involved immunomodulatory or immunosuppressive agents. We should soon see trials of neuroprotective agents. For the immunomodulating agents, the basis of the trials often comes from either animal models, such as experimental allergic encephalomyelitis, or from other therapeutic areas where there is a proposed autoimmune pathogenesis, such as rheumatoid arthritis or Crohn's disease. This strategy centers on altering the immune response to a more suppressive bias, i.e., from Th1 to Th2 or from helper cytokines to suppressive cytokines. Such an approach has advantages over a more generalized immunosuppressive approach, but there are ongoing and planned immunosuppressive strategies, as well. Recent results suggest that such translation is not without some hazard and the need to assure that an agent does not worsen MS is paramount. The problem lies, in part, with our limited understanding of the full mechanisms underlying the production of flare ups and deficit production in MS, such that therapeutic approaches considered potentially beneficial have turned out to produce the opposite result, e.g., anti-TNF directed therapies. Therefore, safety assessments must not only look for adverse events from an experimental agent but also assess whether the agent might have a negative effect on disease course. This can be monitored by either the relapse rate (looking for an increase), change in level of disability (a more difficult outcome to monitor in phase II trials) or increase in MRI activity. The latter is the easiest to accomplish, for the reasons detailed below, and has been utilized as a primary outcome measure in safety trials of combination therapy in MS. The logical basis for this is that most current MS therapies produce a reduction in the number of gadolinium enhancing lesions. Therefore, if the addition of another immunomodulating agent produced an increase in the number of gadolinium enhancing lesions would indicate an adverse interaction between the two agents.

For relapsing-remitting MS, phase II trials most commonly measure a relative reduction in gadolinium enhancing lesion activity as the indication of efficacy. As gadolinium enhancing lesions occur 6-10x as frequently as clinical exacerbations, they provide greater power for detecting differences. This power,

through frequent scanning, provides for an ease of detection and a need for smaller numbers of patients than a clinical outcome would require. In such trials, relapse rate reduction is an important secondary outcome. As these trials usually are of six months duration, changes in EDSS are less likely to be seen. Use of gadolinium enhanced lesions is only reasonable when the putative mechanism of action of the tested agent is expected to impact on the blood-brain barrier (BBB). Such would be the case with most anti-inflammatory agents and adhesion molecule blockers. Agents that might act away from, or independent of the BBB or that might not affect inflammation should have outcome measures that either reflect a clinical change, such as relapse rate, or use MRI metrics that relate to tissue damage.

In primary progressive (PP) or secondary progressive (SP) MS, phase II trials should also aim for a clinical outcome or change in an MRI metric of tissue damage, such as atrophy, T1 black hole volume, NAA spectroscopy or magnetization transfer imaging. Except for early SP MS where there may be concomitant frequent relapses, gadolinium enhancement would not be useful, nor would measures of relapse rate. One difficulty in trying to alter progressive disease lies in the clinical measurement of progression of disability. The commonest scale, the Kurtzke expanded disability status scale (EDSS) is rather insensitive, requires a minimum of six months to demonstrate a change, is weighted heavily toward ambulation and is not linear. A newer scale, the Multiple Sclerosis Functional Composite (MSFC) has several advantages over the EDSS, including linearity, need for fewer subjects to achieve the same power, and less variability, but, as opposed to the EDSS, has not yet been accepted as an outcome measure by regulatory authorities.

II.1 Outline of a typical development plan

A typical phase II trial testing an anti-inflammatory agent in RR MS will utilize a multicenter, randomised, double blind, placebo-controlled, parallel group design.

II.2. Short term studies

II.2.A. Objectives

To evaluate short term efficacy and safety of immunomodulatory or anti-inflammatory drug.

II.2.B. Primary Endpoints

Cumulative total number of enhancing lesions on all post Gd T1 weighted MRI images from monthly scans performed from week 0-12 to week 24-36. Other endpoints related to MRI disease activity can be selected as primary endpoints (see secondary endpoints).

II.2.C. Secondary Endpoints

MRI parameters:

- a. number of new enhancing lesions
- b. total volume of enhancing lesions
- c. number of new T2 weighted lesions
- d. number of T2 weighted lesions
- e. total volume of T2 weighted lesions
- f. number and volume of T1 weighted hypointense lesions
- g. other MRI parameters such as progression of brain atrophy, or variation of magnetisation transfer ratio parameters, (these last parameters particularly useful when testing a non anti-inflammatory drug).

Clinical parameters:

- a. Related to clinical relapses: number of relapses, relapse rate, time to first relapse, number of relapse-free patients

- b. Related to disability progression: number of patients with a predefined interval EDSS progression (usually EDSS score ≥ 1), variations of MSFC scores.

Safety and tolerability parameters: incidence and prevalence.

II.2.D. Exploratory endpoints

Exploratory endpoints must be added according to the pharmacological properties of the drug.

II.2.E. Study design

Multicenter, randomised, double blind, placebo-controlled, parallel group design, is used, the number of arms depending on the different dosages which are evaluated. A screening phase is generally required, 4-12 weeks, with 1 or 2 MRI examinations for selecting MRI active patients. Enrichment of the population study with only MRI active patients enhances the power of the study and reduces the number of patients required. The duration of the study varies between 24 to 36 weeks, depending on the onset of monthly MRI evaluation. In some trials patients are evaluated monthly from baseline, but sometimes, when the full effect of the drug is delayed, patients are evaluated from 12th week to 36th week. A longer period of evaluation is not possible with a placebo arm. Such a design becomes more difficult to perform than a few years ago for ethical reasons and availability of MS patients.

Medication permitted is corticosteroid treatment for MS relapses: 1g methylprednisolone over 3 hours IV infusion/day for 3 or 5 days is usually the recommended treatment of severe relapses.

All symptomatic treatments such as antispastic, anticholinergic, antidepressant, antiepileptic drugs and rehabilitation are usually permitted.

II.2.F. Study Population

Sufficient data are available to calculate accurately the number of patients required for the study according to the anticipated drug effect. As an example, 60 patients per group would be sufficient over 6 months to detect a 50% difference with power taken as 90% and a type one error =0.05 based on the hypothesis of 2.8 ± 3.7 new Gd enhancing T1 weighted lesions (see Sormani et al.).

II.2.G. Specific Inclusion Criteria

- a. Patients who meet the diagnosis criteria for MS according to guidelines provided by McDonald et al.
- b. Patients who present at least one T1 weighted Gd enhancing lesion on MRI performed in the screening period.
- c. Patients with clinical disability measured by EDSS score between 0 and 5.5 inclusive.
- d. Male and female MS patients aged between 18 – 55 years. Women must use an effective method of contraception if they are childbearing potential.

II.2.H. Specific Exclusion Criteria

- a. Patients who present a progressive evolution course defined as a sustained progression of disability evaluated by EDSS score in the year preceding the screening period.
- b. Patients with relapse in the 2 months period preceding baseline. This period may vary according to the drug.
- c. Patients with previous treatment with immunosuppressive, immunomodulating or any investigational drug. According to this previous treatment and the drug tested, exclusion must be complete or a wash-out period of variable duration may be accepted.
- d. Usual exclusion criteria such as patients with concomitant severe or unstable non neurological disease which would induce any risk for the patient.
- e. Pregnant or breastfeeding women.

II.2.I. Specific criteria for early withdrawal and discontinuation

A list of withdrawal criteria is pre-established such as the following: consent withdrawn, severe progression of the disease requiring recommended treatments, serious adverse event other than a relapse, insufficient compliance to the treatment, inadequate concomitant therapy, occurrence of pregnancy.

II.2.J. Data analysis methods

For efficacy analysis the primary population is the intention to treat (ITT) population. The secondary populations is the per protocol population with no major protocol deviation. For safety analysis the exposed population is analysed. Multiple statistical methods are usually used for the primary and secondary end points. The tests are usually two-sided with a global type I error, $\alpha, \leq 0.05$. These methods, adapted to the parameters analysed, must be predefined when the protocol is designed.

II.2.K. Extension studies

The goal of phase 2 studies are: confirmation of “a proof of concept” and/or safety requirements. In the majority of cases, these controlled trials are randomized against placebo, which forbids a long term study. There is no guideline to recommend for managing the patients at the end of the treatment period, the positions of ethical committees varying from country to country.

II.3. Phase 2 studies in primary progressive MS

PPMS remains the only subtype of MS for which there is no approved disease modifying therapy. Immunomodulators and immunosuppressive therapies are used in relapsing secondary progressive MS but these compounds are not effective in SP with sustained progression without relapses, which is similar to PPMS.

Tolerability and efficacy phase 2 studies are randomized, double blind, placebo controlled trials. MRI outcomes are not accepted as surrogate outcomes for phase 2 studies in PPMS Therefore the primary outcome generally used is the time to sustained treatment failure as defined by progression on disability scale, usually EDSS or a more sensitive scale, MSFC.

Some secondary MRI outcomes are available such as the measurement of progression of brain atrophy. The duration of the treatment period is 2 years. Methodology is as the whole similar to the phase 2 trials in RRMS.

III. PHASE III STUDIES FOR REGISTRATION OF NEW DISEASE MODIFYING DRUGS

III.1. Long-term studies to slow or halt relapsing-remitting MS

III.2. Outline of a typical developmental plan

A clinical developmental plan will include at least one large phase III study with a clinical primary efficacy outcome, either relapse rate or disease progression, with a study duration of at least 2 years. The pivotal trial for registration purposes has hitherto included one large well-conducted placebo-controlled trial. Initially, both the U.S. Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMA) have granted approval after one adequate and well controlled trial in patients with relapsing-remitting MS. However, for the latest approved disease-modifying drug in the United States, approval was granted after one large placebo-controlled trial and a short-term comparative trial with the brand leader. In relapsing-remitting multiple sclerosis placebo-controlled trials have become increasingly difficult to perform after approval of several disease modifying drugs for treatment of the disease activity. There are both ethical and practical issues involved. The ethical problems regarding

placebo-controlled trials in relapsing-remitting multiple sclerosis are in principal identical for phase II and phase III trials, whereas the practical problems with enrolment of large patient numbers for prolonged studies are by far more pronounced in phase III studies. Regarding ethical issues for future placebo-controlled clinical trials an international taskforce of clinicians, statisticians, ethicist and regulators concluded that placebo-controlled clinical trials in forms of multiple sclerosis for which partially effective therapies exist were ethical as long as study subjects were fully appraised of the availability of such therapies and were encouraged to pursuit them outside of a clinical trial. Patients who declined to utilise available treatment after proper education and counselling, or those that failed all therapies can be considered to have no treatment alternatives and thus may participate in a placebo-controlled trial. Future requirements for approval of new disease modifying drugs in relapsing-remitting MS by the FDA or EMEA are not known. A developmental plan may include both superiority head to head trials and non-inferiority trials against an established approved drug. Regulatory authorities have not yet approved placebo-controlled trials with historical placebo-controls.

III.2.A. Objectives

To evaluate the efficacy and safety of the investigational drug as mono-therapy in patients with relapsing-remitting multiple sclerosis.

III.2.B. Primary Endpoints

The primary endpoint should be clinical. Time to progression in disability should be preferred in trials of 2-3 years duration. Progression is usually measured as increase of one full (1.0) step on Kurtzkes EDSS scale (0.5 step in patients with a baseline EDSS of 5.5 or above). Progression should be confirmed at 2 assessments with an interval of 3 or 6 months. Alternatively the multiple sclerosis functional composite (MSFC) be used, but this so far has no been accepted as a valid primary endpoint by regulatory authorities, mainly because it has not yet been defined how progression is measured on this scale, and how worsening on this scale should be explained clinically. Changes in the annual relapse rate can also be used as primary endpoint. Registration of confirmed relapses is preferred to the use of reported relapses with or without confirmation.

III.2.C. Secondary Endpoints

If progression is used as the primary endpoint, the annual relapse rate should be included as secondary endpoint, and vice versa. A surrogate marker, MRI, should always be included as secondary endpoint. Gadolinium-enhancing lesions on T1-weighted images, new disease activity on T2-weighted images or combined unique activity (CUA), i.e. a combination of new or enlarging T2-lesions and gadolinium positive lesions, are recommended. Alternatively, changes in T2-lesion area or T1-lesion area (black holes) can be used. Recently, a brain atrophy measure e.g. the brain parenchymal fraction has gained use as a MRI secondary endpoint.

III.2.D. Exploratory Endpoints

Clinical exploratory endpoints are time to first relapse, proportion of relapse-free patients, integrated disability status score (IDSS), i.e. the area under the disability time curve, proportion of patients with progression, and time to EDSS 6 or 7. Exploratory MRI endpoints include some of the MRI endpoints measured under secondary endpoints, gadolinium enhancing lesions, and new magnetic resonance techniques like magnetisation transfer ratios and magnetic resonance spectroscopy.

III.2.E. Study design

A randomised double-blind, placebo-controlled parallel group design is used. The trial involves a baseline evaluation with control for fulfilling of inclusion and exclusion criteria. Patients should be assessed clinically with intervals of 3 months and in case of an acute relapse. Assessment includes scoring on the expanded disability status scale (EDSS) and/or the multiple sclerosis functional composite (MSFC) scale. MRI measures should be obtained at yearly intervals or at least at baseline and

study end. The duration of the study should be at least 2 years and preferably 3 years, if disease progression is the primary endpoint.

III.2.F. Planned sample

The sample size depends on the chosen minimal relevant deficit in the primary endpoint. Typically a sample size of above 300 patients per treatment-arm is required to detect 30-40% difference between the trial-arms with an 80% power and a type 1 error (two-sided) of 5%.

III.2.G. Study population

Patients with relapsing-remitting multiple sclerosis according to accepted criteria (McDonald criteria or Poser criteria) and age 18-55 years. Only patients with low or moderate disability (EDSS \leq 5) should be included. Enrolled patients should have suffered recent disease activity, usually in the previous year, either clinical activity or MRI activity.

III.2.H. Specific inclusion criteria

Similar to those described for phase II placebo-controlled trial.

III.2.I. Specific exclusion criteria

Similar to those described for phase II placebo-controlled trial.

III.2.J. Specific criteria for early withdrawal and discontinuation

Placebo-controlled trials should include exit (escape) criteria defined as significance disease progression, e.g. 2 steps on EDSS, or frequent and severe relapse activity.

III.2.K. Data analysis methods

The analysis of the primary efficacy variable is based on the intention-to-treat (ITT) population. Time to progression is analysed using the log-rank test and Kaplan-Meier estimates.

IV. COMPARATIVE STUDIES

IV.1. Superiority studies

Criteria for conducting comparative superiority trials in relapsing-remitting multiple sclerosis have not been defined. There is currently no international gold standard for such trials. Below is an example that was accepted by the U.S. Food and Drug Administration as additional trial to a placebo-controlled study for approval of a disease-modifying agent. It has to be recognised that this study has been criticised in the medical and scientific community, mainly because its length was thought to be suboptimal.

IV.1.A. Objectives

To evaluate the comparative efficacy and tolerability of the investigational drug versus an approved active control in relapsing-remitting multiple sclerosis.

IV.1.B. Primary endpoints

Proportion of patients who remained relapse-free at 24 weeks.

IV.1.C. Secondary endpoints

Mean number of relapses per patient during 24 weeks, number of active lesions per patient per scan at 24 weeks on MRI.

IV.1.D. Exploratory endpoints

Mean number of combined unique activity lesions, i.e. a combination of new or enlarging T2-lesions and gadolinium positive lesions, per patient per scan, mean number of T1 active lesions per patient per scan, mean number of T2 active lesions per patient per scan, proportion of relapse-free patients at 48 weeks.

IV.1.E. Study design

A randomised parallel-group, single-blind study. Patients and treating physicians were aware of treatment allocation, whereas the evaluating neurologist and radiologist were blinded to study treatment. Ideally, the study should be double-blind but this might be difficult to achieve depending on the characteristics of the drugs under study. The primary efficacy endpoint was assessed at 24 weeks but the study was continued for 48 weeks.

IV.1.F. Planned sample

A sample size of 280 patients per treatment arm provided a 95% power at a significance level of 5% to detect a 30% relative increase in the primary endpoint.

IV.1.G. Study population

Patients with relapsing-remitting multiple sclerosis according to Poser criteria and age 18-55 years. Only patients with EDSS 0 to 5.5 and 2 relapses in the prior 2 years were included.

IV.1.H. Data analysis method

The analysis of the primary efficacy variable was based on the intention-to-treat (ITT) population. The primary end point, the odds ratio for remaining relapse free at 24 weeks, was analyzed by logistic regression with adjustment for treatment and centre.

IV.2. Non-inferiority studies

IV.2.A. Objectives

To evaluate the efficacy and tolerability of the investigational drug in patients with relapsing-remitting multiple sclerosis in comparison with an established drug at fully effective dosage under mono-therapy conditions.

IV.2.B. Primary endpoints

Primary endpoints for such studies have not been defined but should be a clinical measure assessed in the per-protocol (PP) population. Possible primary endpoints would include time to first relapse, proportion of relapse-free patients, annual relapse rate or time to progression on expanded disability status scale (EDSS).

IV.2.C. Secondary endpoints

Clinical endpoints include: Time to first relapse, relapse-free patients, annual relapse rate, time to progression on EDSS confirmed at 6 months, proportion of patients with progression.

MRI endpoints include: New disease activity on T2-weighted images or combined unique activity (CUA), e.g. a combination of new or enlarging T2-lesions and gadolinium positive lesions. Alternatively, changes in T2-lesion area, T1-lesion area (black holes), or brain atrophy can be used.

IV.2.D. Study design

The trial may be a multi-centre, double-blind, randomised parallel-group design with a double dummy technique comparing the investigational drug with the best reference treatment at optimised dosage. The double-blind phase may be followed by an open-labelled extension study.

IV.2.E. Planned sample

The authors are not aware of widely accepted sample size calculations for this type of study; it has to be recognised, however, that by concept non-inferiority studies involve a huge number of patients

IV.2.F. Study population

Patients with relapsing-remitting multiple sclerosis according to accepted criteria (McDonald criteria or Poser criteria) and age 18-55 years. Only patients with low or moderate disability (EDSS \leq 5) should be included. Enrolled patients should have suffered recent disease activity, usually in the previous year, either clinical activity or MRI activity.

IV.2.G. Specific criteria for early withdrawal or discontinuation

Placebo-controlled trials should include exit (escape) criteria defined as significance disease progression, e.g. 2 steps on EDSS, or frequent and severe relapse activity.

IV.2.H. Data analysis method

In non-inferiority trials, analysis of the primary efficacy variable is made on the per-protocol (PP) population. Relapse-free rates or progression-free rates may be compared by a logistic regression model whose 95% confidence interval computation may include baseline characteristics as factors.

V. SECONDARY PROGRESSIVE MS

V.1. Outline of a typical developmental plan

The benefit of disease modifying therapies in patients with secondary progressive MS is less apparent. The results in the European study with interferon-beta 1b showed a modest slowing of progression in secondary progressive MS patients of whom many had relapses. By contrast, no effect on disability progression was observed in the North American study of interferon-beta 1b or in the SPECTRIMS study with interferon-beta 1a. In another study with interferon-beta 1a, the IMPACT study, only an effect on the MSFC was found. Hence, it can be concluded that placebo-controlled double-blind trial are still ethical and feasible in patients with secondary progressive multiple sclerosis. Patients with secondary progressive MS who have still relapses should be informed about the possibility of starting with an approved drug outside a clinical trial, and only patients who have declined to do so should be included in clinical trials.

V.2. Placebo-controlled trials

V.2.A. Objectives

To evaluate the efficacy and safety of the investigational drug as mono-therapy in patients with secondary progressive multiple sclerosis.

V.2.B. Primary endpoints

The primary endpoint should be clinical. Time to progression in disability should be preferred in trials of 2-3 years duration. Progression is usually measured as increase of one full step on Kurtzkes EDSS scale (0.5 step in patients with a baseline EDSS of 5.5 or above). Progression should be confirmed at 2 assessments with an interval of 3 or 6 months. In the future the multiple sclerosis functional composite (MSFC) might provide a useful alternative, but so far this scale has not been accepted as primary outcome measure by regulatory authorities.

V.2.C. Secondary endpoints

The annual relapse rate should be included as secondary endpoint. A surrogate marker, MRI, should always be included as secondary endpoint. New disease activity on T2-weighted images or combined unique activity (CUA), e.g. a combination of new or enlarging T2-lesions and gadolinium positive lesions

or brain atrophy e.g. measured as the brain parenchymal fraction, are recommended. Alternatively, changes in T2-lesion area or T1-lesion area (black holes) can be used.

V.2.D. Exploratory endpoints

Clinical exploratory endpoints are proportion of patients with progression, and time to EDSS 6 or 7, integrated disability status score (IDSS), e.g. the area under the disability time curve, time to first relapse, proportion of relapse-free patients. Exploratory MRI endpoints may include some of the MRI endpoints measured under secondary endpoints, gadolinium enhancing lesions, and new magnetic resonance techniques like magnetisation transfer ratios and magnetic resonance spectroscopy.

V.2.E. Study design

A randomised double-blind, placebo-controlled parallel group design is used. The trial involves a baseline evaluation with control for fulfilling of inclusion and exclusion criteria. Patients should be assessed clinically with intervals of 3 months and in case of an acute relapse. Assessment includes scoring on the expanded disability status scale (EDSS) and/or the multiple sclerosis functional composite (MSFC) scale. MRI measures should be obtained at yearly intervals or at least at baseline and study end. The duration of the study should be at least 2 years and preferably 3 years, if disease progression is the primary endpoint.

V.2.F. Planned sample

The sample size depends on the chosen minimal relevant deficit in the primary endpoint. Typically a sample size of above 300 patients per treatment-arm is required to detect 30-40% difference between the trial-arms with an 80% power and a type 1 error (two-sided) of 5%.

V.2.G. Study population

Patients with secondary progressive multiple sclerosis according to accepted criteria and age 18-55 years. Only patients with moderate disability (EDSS 3 to 5.5) should be included. Enrolled patients should have suffered recent clinical disease activity, i.e. progression or relapses during the last 1-2 years.

V.2.H. Specific inclusion criteria

Similar to those described for phase II placebo-controlled trial.

V.2.I. Specific exclusion criteria

Similar to those described for phase II placebo-controlled trial.

V.2.J. Specific criteria for early withdrawal and discontinuation

Placebo-controlled trials should include exit (escape) criteria defined as significance disease progression, e.g. 2 steps on EDSS.

V.2.K. Data analysis methods

The analysis of the primary efficacy variable is based on the intention-to-treat (ITT) population. Time to progression is analysed using the log-rank test and Kaplan-Meier estimates.

VI. PRIMARY PROGRESSIVE MS

VI.1. Outline of a typical developmental plan

The clinical course in primary progressive MS is characterized by a progressive accumulation of neurological deficits from onset without relapses. There is no approved therapy for this course of multiple sclerosis.

A clinical developmental plan will include at least one large phase III study with disease progression as the clinical primary efficacy outcome, and with a study duration of at least 2 years.

VI.2. Placebo-controlled trials

VI.2.A. Objectives

To evaluate the efficacy and safety of the investigational drug as mono-therapy in patients with secondary progressive multiple sclerosis.

VI.2.B. Primary endpoints

The primary endpoint should be clinical, and time to progression in disability should be preferred in trials of 2-3 years duration. Progression is usually measured as increase of one full step on Kurtzkes EDSS scale (0.5 step in patients with a baseline EDSS of 5.5 or above). Progression should be confirmed at 2 assessments with an interval of 3 or 6 months. Alternatively the multiple sclerosis functional composite (MSFC) may be used, but it has not yet been approved as primary outcome measure.

VI.2.C. Secondary endpoints

A surrogate marker, MRI, should always be included as secondary endpoint. The currently recommended measures for therapeutic trials in relapsing remitting and secondary progressive multiple sclerosis show only little change in primary progressive multiple sclerosis and therefore more pathologically specific MRI measures may be required. Changes in T1-lesion area (black holes), brain atrophy, e.g. measured as the brain parenchymal fraction or cervical cord cross-sectional area may be used.

VI.2.D. Exploratory endpoints

Clinical exploratory endpoints are proportion of patients with progression, and time to EDSS 6 or 7. Exploratory MRI endpoints may include some of the new magnetic resonance techniques like magnetisation transfer ratios and magnetic resonance spectroscopy.

VI.2.E. Study design

A randomised double-blind, placebo-controlled parallel group design is used. The trial involves a baseline evaluation with control for fulfilling of inclusion and exclusion criteria. Patients should be assessed clinically with intervals of 3 months and in case of an acute relapse. Assessment includes scoring on the expanded disability status scale (EDSS) and/or the multiple sclerosis functional composite (MSFC) scale. MRI measures should be obtained at yearly intervals or at least at baseline and study end. The duration of the study should be at least 2 years and preferably 3 years, if disease progression is the primary endpoint.

VI.2.F. Planned sample

The sample size depends on the chosen minimal relevant deficit in the primary endpoint. It has been reported that in secondary progressive multiple sclerosis, a sample size of above 300 patients per treatment-arm is required to detect 30-40% difference between the trial-arms with an 80% power and a type 1 error (two-sided) of 5%. However, such information is currently not available for primary progressive multiple sclerosis.

VI.2.G. Study population

Patients with primary progressive multiple sclerosis according to accepted criteria and age 18-55 years should be studied. It is a problem that patients with primary progressive multiple sclerosis do not readily conform to accepted criteria (McDonald criteria or Poser criteria) and have a wide differential diagnosis. Only patients with moderate disability (EDSS 3 to 5.5) should be included. Enrolled patients should have suffered recent clinical disease activity, i.e. progression or relapses during the last 1-2 years.

VI.2.H. Specific inclusion criteria

Similar to those described for phase II placebo-controlled trial.

VI.2.I. Specific exclusion criteria

Similar to those described for phase II placebo-controlled trial.

VI.2.J. Data analysis methods

The analysis of the primary efficacy variable is based on the intention-to-treat (ITT) population. Time to progression is analysed using the log-rank test and Kaplan-Meier estimates.

VII. OTHER STUDIES (ATYPICAL MS FORMS)

Rare inflammatory demyelinating syndromes, such as Marburg' Disease, Pseudotumoral forms, Balo's Concentric Sclerosis (BCS) or Devic's Neuromyelitis Optica (DNO), are difficult to be studied in a randomised controlled clinical trial mainly due both to absence of specific clinical and laboratory findings leading to an early and definitive diagnosis and to the small number of patients seen every year with homogeneous clinical characteristics (for example at the onset of disease, after a few clinical relapses and low disability). As a consequence, to date no reliable data are available on the efficacy of immunomodulatory or immunosuppressive drugs, usually used in MS, in halting or slowing the inflammatory and degenerative processes underlying these rare inflammatory diseases.

VII.1. Marburg's disease

Marburg's disease is an acute malignant monophasic demyelinating disease, which usually results in death within a few weeks or months after the initial bout. It is characterized by widespread and progressive cerebral white matter destruction or by severe pathological involvement of clinically strategic regions such as brainstem, resulting in bulbar paralysis. Short-term, observational studies of a restricted cohort of patients evaluating the therapeutic efficacy of the association of high dosage Metilprednisolone and frequent, pulse administration of immunosuppressive drugs (cyclophosphamide or mitoxantrone) or plasmapheresis (with or without subsequent pulse cyclophosphamide) have been reported.

VII.2. Balo's Concentric Sclerosis and Pseudotumoral forms

Balo's Concentric Sclerosis is a rare demyelinating disorder characterized pathologically by concentric rings of alternating demyelinated and relatively myelin preserved white matter. The pathogenesis of the concentric lesion may be explained by periodic suppression of demyelination in a rapidly expanding area of inflammation, allowing remyelination or only transient incomplete demyelination to occur. While initial reports of BCS predicted that the disease was rapidly progressive and fatal, a good prognosis has been recently described in a few cases and the lesion is usually considered as an atypical, large, pseudotumoral MS plaque. Large, focal, tumor-like demyelinating lesions of the CNS often represent a diagnostic challenge, which reasonably calls for a stereotactic biopsy, particularly when isolate in the brain, to exclude glioma, infectious processes or primary CNS vasculitis. These cases are usually characterized by a severe course and a rapid clinical deterioration. Response to therapy is highly variable. Patients are usually treated with steroid, generally in high doses intravenously, as well as variously with cyclophosphamide or plasma exchange. Despite the aggressive therapy sometimes the disease ultimately progresses, mainly in patients with spinal cord involvement.

VII.3. Devic's Neuromyelitis Optica (DNO)

DNO is usually considered as a distinct disease entity from Ms according to several clinical, neuroradiological and CSF findings. Pathological aspects and the relevant pathogenetic role of humoral immunity also support the belief that DNO may be a separate syndrome. DNO diagnosis is difficult to make after the first episode. Two or more acute episodes of neurological impairment involving the optic nerves and the spinal cord, in a simultaneous or sequential temporal relationship, must be observed, with no clinical or MRI evidence of brain involvement. A poor prognosis may be predicted by the age at onset, the interval between first and second episode, the relapse rate and the severity of the first attack. At the moment no effective treatment has been demonstrated, although chronic or pulse steroid therapy is often used in DNO

patients, associated with a variety of immunosuppressive or immunomodulatory agents, empirically chosen, usually after 3-5 attacks have occurred.

VII.4. Future therapeutic strategies

New emerging disease-modifying therapies that target cytokines, the blood brain barrier, the “trimolecular complex” or that act by deletion of auto-reactive T cells are candidates for treatment of these rare MS variants and their efficacy and safety should also be evaluated. These syndromes are characterised by a very aggressive course, therefore the research of active and efficacious treatments needs to be strongly encouraged. Since most of these patients have usually a bad prognosis and deteriorate to severe irreversible disability in only a few months or years, beneficial effect due to therapeutic intervention may be easily detected by using strong primary end points, such as death or loss of deambulation. Classical phase II-III studies are impossible in this MS variants; small group of patients treated and monitored with a specific protocol are the only feasible approach, even if it implies problems with interpretation and generalization of the results.

The Restricted Cohort Study applies the principles and patient enrolment procedures regularly used in randomised clinical trials. Therefore, strict eligibility criteria and the appropriate choice of zero time must be well defined; anyway baseline differences should be adjusted for prognostic risk. In addition, patients must be classified according to suitable clinical criteria to enable adjustment for any inequalities in susceptibility to the outcome. Finally, the analysis of the data should be conducted using the same methodology used in clinical trials.

The primary objective of these studies is to provide preliminary data on the efficacy, considered both on short term evolution of the recent clinical attack as well as on long term evolution of the disease, evaluated as confirmed changes of EDSS and ambulation index. MRI and neurophysiological test are very important to support clinical observation. The secondary objectives of these studies are to gather descriptive information concerning short and long term tolerability and safety of the investigational therapeutic intervention as well as about the potential loss of efficacy on long-term chronic or pulse administration.

VIII. EXAMPLES OF PHASE III TRIALS IN MULTIPLE SCLEROSIS

Pivotal placebo-controlled trials in relapsing remitting multiple sclerosis

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Phase III placebo-controlled trials in secondary multiple sclerosis

1. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. *Lancet* 1998;352:1491-1497.
2. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: Clinical results. Secondary Progressive Efficacy Clinical Trial of Recombinant Inteferon-beta-1a in MS (SPECTRIMS) Study Group. *Neurology* 2001;56:1496-1504.

IX. SUGGESTED READINGS

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