SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

EFFICACY OF IMMUNOMODULATORY TREATMENT AND EVALUATION OF CEREBROVASCULAR HEMODYNAMIC CHANGES IN MULTIPLE SCLEROSIS

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Efficacy of immunomodulatory treatment and evaluation of cerebrovascular hemodynamic changes in multiple sclerosis

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The Examination takes place at Department of Neurology, Faculty of Medicine, University of Debrecen,
at 11.00 a.m. 7th of September, 2015.

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
at 13.00 p.m., 7th of September, 2015.

1. Introduction, overview of literature

Multiple sclerosis (MS) is a chronic, progressive, multifocal inflammatory disease of the central nervous system (CNS), affecting 2-3 million patients in the word, and approximately 6-10000 people in Hungary. Typical feature of the disease is presence of multifocal demyelinating plaques in the central nervous system, which are results of autoimmun inflammatory attack against the myelin sheet. Damage of myelin will cause degeneration of axons, and axonal damage will be responsible for the progressive disease course and for the severity of neurological disability. Primary degenerative form of the disease is also possible, wherein degeneration of oligodendrocytes or neurons can be the first step, and released molecules from the damaged cells can evoke secunder immunreaction and inflammation. There are different genetic and environmental factors in the background. Particular environmental factors in a genetically susceptible person during a determinated period of life, probably before adolescence, can provoke the disease, and it will be clinically manifest later on. However the clinical picture and the disease course are also highly variable. 65-80% of

patients have relapses and remissions in the begining (relapsing-remitting form). Exacerbation was defined as a rapid progressive worsening of symptoms or development of a new neurological deficit lasting more than 24 hours. Any kinds of neurological symptom can come unexpectedly, either alone or in combination. Symptoms can disappear after the relapse or may become residual and cause permanent neurological deficit. After several years patients experience slow gradual progression of symptoms instead of acut relapses, what is called as secunder progressive phase (SP-MS). In 10-15 % of patients slowly accumulating disability can be detectable from the begining without acut exacerbations, this is the primary progressive form of the disease. MS specific clinical sign, laboratory, electrophysiological or other diagnostic abnormality is not existing. For the diagnosis of MS, chronic and multiple involvement of the CNS should be proven according to the McDonald criteria: 1. dissemination of the disease in time, 2. in space and 3. other neurological condition in the background can be excluded. In the clinical practice methylprednisolone is used for the treatment of exacerbations in 1 g /day for 3-5 days in infusion intravenously. Steroid does not influence patients' long term

disability outcome after the acute effect. Immunomodulatory treatment (IMT) inhibit the inflammation in the CNS and reduces the extent of axonal damage and this way they can decrease the frequency and severity of relapses and postpone the occurance of significant disability. Neuroprotective drugs are not available in MS. IMT are the most effective in the relapsing-remitting phase of the disease, what is dominated by inflammation and less effective in the degenerativ, progressive phase. Today there are 10 approved drugs on the market: 3 different forms of interferon-beta (IFN beta) and glatiramer-acetate (GA), 3 oral agents, as a fingolimod, teriflunomid and dimetil-fumarate, the monoclonal antibodies natalizumab and alemtuzumab, and finally the immunsuppressive mitoxantrone, which is also used in oncology as well as an antitumor agent. Clinical efficacy of the drugs can be evaluated by frequency and severity of exacerbations (relapse rate: mean number of relapses related to one patient from a patients'group during a year) and by different functional evaluating scales.

There is not significant difference in efficacy of IFN betas and glatiramer-acetate. All drugs are used in RR-MS patients, who are still able to walk, and drugs reduce the relapse rate with

approximately 30 % compared to placebo. The period of treatment cannot be predicted, in case of good respone, the administration of the drug should be continued for years, until the secondary progressive phase has been developed.

Up to now there is not existing a well accepted, international, treatment guideline, which involves the newer therapeutic agents as well, because we do not have enough experiences, data from comparative studies to create a good recommendation. Based on the heterogenity of MS, the therapeutic purpose is initiation of personalized treatment. The administration of newly accepted drugs are restricted based on theirs efficacy and safety on long term period. The more therapeutic options come together with the need of more precise monitoring of efficacy, therefore newer and newer clinical and radiological endpoints are used, making the choice among different therapies easier.

Damage of the vegetative nervous system has not got too much attention both in the clinical practice and different studies as well.

Cardiovascular (orthostatic intolerance, arrhytmia, diminished cardiovascular reflexes), termoregulation or pupillar abnormalities are seldom recognised, and relationship with the other symptoms has

not fully clarified yet. Based on the literature from the previous years sympathetic dysfunction comes first and parasympathetic abnormalities are later consequences of the progressive disease. Sympathetic dysfunction can be detectable in the begining of the disease course, even in case of clinically isolated syndrome (CIS), when only one single MS related clinical episode occures. Severity and occurance of parasympathetic dysfunction correlates with the duration of the disease and with the extent of spinal cord atrophy on the MRI, which is a good marker of axonal loss. Although the pathophysiology behind these symptoms is not fully clarified, demyelinated plaques may cause disruption to reflex pathways in crucial areas including the brainstem, spinal cord, hypothalamus, limbic system, and frontal cortex. It is known from MR studies, that MS is a diffuse central nervous system disorder, with significant neurodegenerative component, and there is no relationship between MRI parameters and the clinical status of the patients. Although these manifestations of autonomic dysfunction are seldom recognized in patients with MS, they may cause serious complications.

Analysis of heart-rate variability (HRV) is good method for evaluation of parasympathetic functions, and monitoring of blood pressure reactions after different stimuli reflects the control of the sympathetic regulations. Cerebrovascular autoregulation is the intrinsic ability of the brain to maintain a constant cerebral blood flow during changes of cerebral perfusion pressure (CPP). Autoregulation monitoring relies on the observation of spontaneous responses of CBF to spontaneous fluctuations in CPP or mean arterial blood pressure (MBP). In case of impaired autoregulation cerebral flow increases or decreases together with the blood pressure.

2. Objectives

- What is the efficacy of the first line used interferons and glatiramer-acetate treatment on the neurological disability on a long term follow-up?
- Is there relationship between the clinical presentation of the disease (unifocal or multifocal) and the treatment response?
- Are there any differences in clinical characteristis of responder and non-responder patients (disability at the time

of treatment initiation, duration of MS, initiation of the treatment in the early or later phase of the disease course)?

- How strong is the therapy adherence and tolerabilty on long term follow-up?
- What kind of side-effects occur on long term immunmodulatory treatment?
- Can the abnormality of the cerebrovascular autoregulation be detected by transcranial Doppler in early MS patients compared to healthy controls?
- If subclinical vegetative abnormality is detectable, is there connection with the results of the clinical scales (EDSS, MSFC)?
- What is the effect of anti-inflammatory methylprednisolone on the autoregulatory mechanisms in case of acute relapse?

3. Patients and methods

The trial protocol was approved by the local Ethical Committee of University of Debrecen. All subjects signed a written informed consent prior to the investigation.

3.1. Inclusion criteria

The IMT has been introduced at our department in 1996 for treatment of RR-MS. We started to treat 12 and 14 patients with IFN beta-1b and GA respectively. Intramuscularly administered (IM) IFN beta-1a has been available since 1999 and subcutaneously (SC) administered IFN beta 1a since 2001. Because the number of treated patients/year was limited by financial suppport, most of the patients had to wait for months or years to start their treatment. In most cases the drug was selected by the central commitee instead of by the treating physicians or patients. A total of 81 RR-MS patients were selected according to the international guidelines for IMT at the Department of Neurology of the University of Debrecen up til the end 2003. Criteria for enrollment were RR-MS, definite MS according to the diagnostic criteria, EDSS score of 0-5.5, age 18-50 years and at least 2 relapses in the last 2 years. Disability status was evaluated every 3 months and in case of relapses. Adverse events and laboratory assesments were controlled monthly when IMT was initiated and later every 3 and 6 months respectively. Based on the type of drugs, patients were divided into different groups. The

number of relapses for the 2 years prior to IMT was compared to the number of relapses after IMT initiation. Relapse-free patients or patients with greater than 50% reduction in the biennial number of relapses were grouped as responders. Patients having an identical or higher relapse rate on IMT were considered nonresponders or patients with 50% or less biennial reduction compared to the 2 years' pretreatment were defined as partial responder. Therapeutic efficacy of the drugs were evaluaed related to following clinical factors: time between onset and diagnosis of MS, time between diagnosis and initiation of IMT, clinical presentation of the disease at onset (unifocal or multifocal), age, relapse rate and disability.

For the examination of the autonomic nervous system thirty patients with short disease duration (mean duration was 6 years) and without significant disability were enrolled from our neuroimmunology clinic Patients were diagnosed as having relapsing-remitting (RR) (n=20), primary-progressive (PP) (n=3) MS according to revised McDonald criteria or clinically isolated syndrome with single MS-related clinical episode (n=7). None of the subjects had any other disease that could have affected cerebrovascular autoregulation (e.g. diabetes mellitus, stroke, thyroid dysfunction). Examinations were

also done in 10 age- and gender-matched healthy persons as a control group. Eleven patients (9 RR-MS, 2 CIS) had acute exacerbations and received 1000 mg methylprednisolone intravenously (iv.) for 5 consecutive days. These subjects were examined before and after the high-dose methylprednisolone treatment (mean time interval: 6 days).

3.2 Tilt-table test

Each subject was examined in the morning after overnight fasting. Caffeine-containing products, alcohol or medications were avoided. Real-time registration of blood flow velocity in both middle cerebral arteries by transcranial Doppler (Multidop X4, DWL Compumedics Germany GmbH), and non-invasive beat-to-beat blood pressure and heart rate monitoring (CNSystems Task Force monitor 3040i) were continued for 10 minutes in the supine position for 30 minutes in a tilted-up position at a 70-degree angle on the tilt table, and for a final 5 minutes after tilting back to the supine position. MCA blood flow velocities were recorded at a depth of 50-60 mm through the temporal bone window using 2-MHz TCD probes.

3.3. Statistical analysis

Statistical analyses related to IMT were carried out using Statistica for Windows (version 5.5, StatSoft, Tulsa, USA). Statistical significance was considered when $p<0,05$. Normality of parameters was checked by Shapiro-Wilk test. Analysis of variance (ANOVA) or Kruskal-Wallis ANOVA was performed to compare continuous variables between subgroups. For categorical data, the Pearson chi-squared test was used.

The method used for assessment of dynamic cerebral autoregulation has been described previously. Mean values of arterial blood pressure (MBP) and cerebral blood flow velocity were averaged over 3-second intervals. From a consecutive 20 such values, Pearson correlation coefficients between MBP and CBF velocity were calculated for each subject and each minute of a 10-minute period. The resulting sets of 1-minute correlation coefficients were then averaged for each subject, yielding the autoregulatory index Mx, reflecting the correlation between MBP and mean CBF velocity. Slopes of the rise in heart rate after tilting up were also examined. Changes in CBF velocity associated with a 1-mmHg increase in MBP after the provocation were estimated using multilevel mixed

effects linear regression. The analysis encompassed both immediate and delayed changes in CBF, ranging from 0 to 12 seconds of lag after the provocation. Lag-by-lag and rolling-summed lag effects were evaluated (lag-by-lag effects refer to the additive change in blood flow velocity in reference to the previous second, specifically for each lag-second; rolling-summed lag effects refer to cumulative changes from the moment of MBP increase up to the given lag-second). For unadjusted between-group comparisons, Student's two-sample t-test, Wilcoxon's rank-sum test, and the Kruskal-Wallis test were used, subject to number of groups compared and distributional assumptions. Unadjusted within-group before-after comparisons were made using Student's paired t-test or Wilcoxon's matched-pairs signed-ranks test, subject to distributional assumptions. Values of $p<0.05$ were considered to indicate statistical significance.

4. Results

4.1 Results of long term follow-up of patients on IMT

Out of 81 patients (51 female, 30 male), 21 were on IFN beta-1b (Betaferon, Shering, Berlin, Germany) 8 million international units

every other day, 26 were on GA (Copaxone, Teva Pharmaceutical Industries, Petah Tikva, Israel) 20 mg every day, 27 were on IM IFN beta-1a (Avonex, Biogen, Cambridge, MA) 30 μg each week and 7 were on subcutaneous IFN beta-1a (Rebif, Serono, Geneva, Switzerland) 44 μg three times a week. None of the patients received other concomitant disease-modifying treatment such as azathioprine or mitoxantrone in this study. Mean time on therapy was 54 (± 33) months. 7 patients discontinued the treatment in the IFN beta-1b and the GA groups. SP-MS developed in 7 cases, 4 in the IFN beta-1b and 3 in the GA group. The IMT was changed in three cases, IFN beta-1b was changed to GA due to lack of efficacy in one case after a year and 1 patient from each group shifted from IFN beta-1b and GA injection to the less frequently injected IM IFN beta-1a due to intolerable local side effects and frequent administration respectively. One IM IFN beta-1a treated patient transiently discontinued the therapy after 2 years due to planned pregnancy. 2 patients developed chest tightness, dyspnea, palpitations and anxiety as systemic postinjection reaction side effects of GA at the 3 months treatment period. One patient died in nontreatment-related GA acute myeloblastic leukemia. Evaluating the treatment response there was

no sex difference. The mean number of relapses decreased by 75% in the total group and was significantly lower in each group, when it was compared with the 2 years' pretreatment. The number of relapses was different among the IMT groups, but there were no significant differences in the mean decline of relapses. (p=0,996). Mean EDSS scores increased by only 0,5 points. The full length of treatment was different in the groups, because different IMTs became available at different times. Therefore we compared the progression by treatment duration with subgroups of 2, 4, and more 6 years' continuous treatment. The total number of patients with more than 6 years' treatment was 29. At the time of initiation of IMT, disability was less pronounced in the IFN beta-1a group, and the difference sustained during the follow-up. The degree of progression in EDSS scores was not different among the groups at 2 or 4 years (p=0,23 or 0,11), and became different only after 6 years (p=0,003). When the dissemination of clinical symptoms was compared to the clinical course and response to IMT, no difference was found between uni- or multifocal clinical appearance in the age of onset of disorder, in the time required for diagnosis of clinically definitive MS, in patients' natural history or change on IMT. Patients with

multifocal symptoms at onset had a higher tendency toward higher EDSS scores at baseline. Checking the difference between responders and nonresponders, we found that age, relapse rate in the pretreatment period, EDSS score at the time of initiation of IMT were not different, like the time interval between onset and diagnosis of definitive MS and the duration of disorder at the time of initiation of therapy. Nonresponders developed higher EDSS scores at the second and fourth years of treatment (p=0,015 and 0,016). Furthermore we found correlation between age at the time of initiation of IMT and elapsed time between onset and diagnosis, time interval between diagnosis and initiation of IMT, relapse rate in the prior 2 years of IMT and disability according to the mean EDSS score at baseline, and after 2, 4 or more than 6 years of treatment. Occurrence of injection-site reactions declined during long term treatment, but flu-like symptoms were consistent in some cases.

4.2. Examination of cerebrovascular autoregulation

Patients' mean age was 35 years, with less than 6 years of disease history on average. None of the patients had significant clinical disability. The mean score was 2,6 ±1,24 on the Expanded Disability

Status Scale (EDSS) and0,054 ± 0,5 on the Multiple Sclerosis Functional Composite (MSFC) instrument. Fourteen patients were on immunomodulatory treatment (interferon-beta or glatiramer-acetate) and one patient received plasmapheresis after the examination because of a severe relapse. None of the subjects had any other concomitant disease that could have affected cerebrovascular autoregulation (e.g. diabetes mellitus, stroke, thyroid dysfunction). The conventional MRI examination showed more than 9 supratentorial lesions in 25 patients, at least one brainstem lesion in 21 cases and spinal cord lesion in 13 cases on T2 weighted images. The Mx index for the correlation between MBP and CBF velocity changes was calculated for the left and right sides separately, and also bilaterally. All results were compared to their counterparts obtained from the control group. Calculations were also carried out stratified for disease subtype. No significant differences were seen in unilateral or bilateral Mx indices between patients and controls before or after provocation by tilting. Similar non-significant Mx index differences were found when comparing patients of various MS subtypes to healthy subjects. No correlation was found between Mx values and EDSS or MSFC results.

Eleven patients suffering from acute exacerbation (9 RR-MS, 2 CIS) were examined before and after intravenous corticosteroid treatment. Clinical improvement was assessed via EDSS and MSFC. The mean [SD] EDSS was 3,59 ± 0,8 before the treatment and decreased to 3,32 ± 0,93 (p=0.084), while MSFC changed from -0,22 ± 0,46 to 0,02 ± 0,57 (p=0.024) during the treatment period. The administration of high-dose methylprednisolone did not cause significant changes in the Mx indices.

Though these analyses did not detect any significant differences between MS patients and controls, more prominent increase in heart rate and a greater decrease in CBF velocity were observed in patients than in controls after head-up tilting. Curves were similarly different after versus before steroid administration, suggesting a tendency of normalization for these parameters. The slope of the upsurge section of the heart rate curve was not significantly steeper in the patient group. However, the slope of tilt-induced heart rate elevation was significantly lower after steroid treatment within the first 8-second time-window after the stimulus (p=0.010); the difference gradually diminished upon extending the slope calculation time-window to 14 seconds where it became of borderline significance (p=0.05).

Finally, changes in CBF velocity associated with a 1-mmHg increase in MBP were modeled. Upon an MBP increase of 1 mmHg, CBF velocity also becomes higher by about 0.5 cm/sec within the same second, followed by quick counter-regulation that produces an overshoot, but eventually CBF velocity returns to the base level. The flow increase after MBP elevation is lower in patients, but the subsequent compensation is more prominent; these differences are statistically significant ($p<0.05$). The differences were also significant when comparing MBP-related CBF velocity changes after steroid administration with the pre-treatment reference.

5. Discussion

5.1. Effect of long-term immunomodulatory treatment

Interferons and glatiramer-acetate are the so-called self-injected (first-line or basic therapy) drugs, patients administer themselves after a person-dependent learning phase according to the drugs administrations route and frequency. Few years ago these were the only therapeutic options for treatment of relapsing-remitting MS. Nowadays with the increasing number of new opportunities, to

choose the right treatment for the right patient in the right time is becoming more and more challenging. Different algorithms can support the choice. Today the accepted strategy is the escalation, which means initiation with the safest but less effective agent and switch to more effective but riskier treatment in case of progression. Self-injected drugs are really safe for long-term use, so they are the first-line drugs in the escalation therapy. Concerning MS treatment our aim is to reach remission, the relapse- and progression-free condition both from the clinical and radiological point of view with the fewest side effects. If the patient is in remission, the treatment should be continued, but with occasional reevaluation. One- or two-third of patients on self-injected drugs never reaches the state of full remission. Quite challenging at decide about switching in case of partial efficacy of the drug, because "escalation therapy" has not been clearly proven yet. We need more and more experiences about the date and way of switching, and how the prognosis is changing with different treatment options. Our objective was the identification of some clinical markers, what can be useful in evaluation of long term efficacy of firs-line immunomodulatory treatment. Efficacy of the therapy was measured by relapse rate, compared to the relapse

rate in the same group before the IMT. According to our results the relapse rate at the 2-year follow-up was reduced by more than 60%, regardless the type of treatment, what is better than the results of double-blind trials, but consistent with results of open-labelled studies. Based on the different inclusion criterias, there is hard to compare the result of clinical trials, but most of them describes similar efficacy in case of interferons. Patients in our study group were quasi-randomized to different IMT, because patient allocation was decided by medication availability, not by patient's or physician's decision. Progression of disability was not different among treatment groups, suggesting similar efficacy of the different agents over the course of the disorder. Increasing number of therapeutic options need more precise monitoring of patient's condition and using newer and newer clinical and radiological endpoints the switching between therapies can be easier. Our finding suggests that the frequency of relapses is an important indicator of the efficacy of IMTs. Different studies emphasized the importance of early treatment, which can also have favorable impact on clinical and MRI parameters during the disease course. In our study, patients receiving IM IFN beta-1a had the lowest disability scores after 6

years' treatment. Later initiation of IFN beta-1b in the disease course can be the reason for that, and during this period patients deteriorated and became more disabled in the IFN beta-1b than the IFN beta 1-a group, with the same disease duration supporting the potential benefit of early treatment. We did not find any difference or prognostic value of unifocal or multifocal presentation of MS onset in the time required to develop clinically definitive MS or to predict treatment response. Similarly to other Hungarian's data, the progression measured by EDSS after 6 years of treatment was less pronounced when the baseline EDSS score was lower. Discontinuation/switch rates were 44% for GA, 36.5% for IFN beta-1b, 20.9% for SC. IFN beta-1a and 18.3% for IM IFN beta-1a showing excellent adherence rate to IMT. The percentage of patients who dropped out of our follow-up study before reaching the secondary progressive phase was remarkably low. The consistent side effects of IMT varied between 10-35%, most frequently associated with SC. IFN administration. Although our group was too small to make strong conclusions, but our patients have mild disability even after 12 years of disease, and demonstrated the benefit of IMT. Nonresponders continuously progressed. In the

literature responder patients are typically older, have longer disease duration and higher relapse rate before treatment initiation, in our study we detected longer disease duration in case of nonresponders patients. It was probably because of the small study group. We have found that measurement of clinical response by evaluation of disability progression and frequency of relapses can be predictable for clinical efficacy in subsequent years. For those with insufficient relapse-rate reduction in the first 2 years of treatment, a different IMT or other therapeutic approaches should be recommended. With combination of the MRI results, the purpose is to reach the disease activity free status. Several papers suggest lateral switch among first-line drugs with different mechanism of action in case of suboptimal effect or presence of disturbing side effects. This type of switching has already been succesfully performed in our clinic too. Until the patient is progression free with the first-line agents, continuation of the treatment is recommended. With high disease activity, when progression is still present after administration of second-line drugs, there are only experimental alternatives or intensive immunosuppression (autologuous hematopoietic stem cell transplantation) as possible therapeutic option.

5.2. Cerebral hemodynamic changes and effect of high-dose corticosteroid treatment

Evaluating the autoregulatory Mx index, our study did not show a significant disturbance of dynamic cerebral autoregulation (dCA) in MS patients, and produced similar correlation estimates between MBP and CBF velocity in healthy persons and MS patients. Beside dCA we also evaluated the dynamic rise in heart rate after provocation, but no significant difference was found in MS patients compared to the control group. In our investigation into the changes in CBF velocity associated with a 1-mmHg increase in MBP, we observed an immediate elevation in blood flow velocity, but 2 seconds later, counter-regulation set in, causing an overshoot of the flow velocity to below the base level. Another counter-regulation occurred in the next second, and the flow velocity gradually reached the base level after 5 seconds. Along the course of the regulation process, significant differences were detected between MS patients and the healthy group.

In our study, 83% of 30 patients had multiple supratentorial lesions by conventional MRI, 70% had brainstem, and 43% had spinal cord location without hypothalamic or gray matter involvement. In fact,

multiple sclerosis is not only a focal, inflammatory demyelinating disease. It is a diffuse central nervous system disease with an important neurodegenerative component, which occurs very early in the course of disease and the correlation between MRI measures of inflammation and neurodegeneration is weak in all disease phases.

In this study the effect of high-dose intravenous. MP on dynamic cerebral autoregulation was also investigated in a subgroup of patients having acute exacerbations, but only a non-significant difference in Mx indices was detected after steroid treatment compared to the pre-steroid results. However, the slope of tilt-induced heart rate elevation was significantly lower after steroid administration within the first 14-second time-window after the stimulus. Looking at a 1-mmHg MBP increase, the effect detected in CBF velocity changes was significantly different after the treatment than before. The difference could be explained by the local changes in blood flow as a major consequence of inflammation. We suppose, that reduced amount of substances, which are presumably released during brain inflammation in multiple sclerosis, altered neuronal activity and local metabolic changes secondary to diminished inflammation and improvement in endothelial cell function and in

blood-brain barrier permeability can be responsible for that. We confirmed that steroid treatment of the acute attack caused clinical improvements assessed by EDSS and MSFC, and reduced inflammation results in significant hemodynamic changes compared to the pre-treatment results. We are aware of the fact that this study is not without limitations. Small number of subjects and heterogeneity of MS in the patient group are fundamental limitations. It is important to emphasize that only CBF velocity was measured by TCD, which only reflects changes in CBF if the MCA's diameter remains constant, and standards for measurement and analysis of dCA are still lacking.

6. New results

1. Evaluation of the relapse rate in the first 2 years after treatment initiation can be eligible for monitoring of long term efficacy of the treatment.
2. We did not find difference in clinical presentation of the disease (unifocal or multifocal) related to therapeutic efficacy.

3. Earlier initiation of interferon beta prevents more the occurence of later disability after longer period of time compared to later administration
4. The adherence to treatment is the best in case of im. IFN beta-1a. Side effects are tolerable.
5. There is no significant abnormality of the cerebrovascular autoregulation in MS patients.
6. After provocation the dynamic rise in heart rate and changes in CBF velocity associated with a 1-mmHg increase in MBP, was found significantly different in MS patients compared to the control group.
7. High-dose intravenous methylprednisolon in relapses decreased the dynamic rise in heart rate and changes in CBF velocity associated with a 1-mmHg increase in MBP was found significantly different in MS patients compared to the pretreatment results.

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List of publications related to the dissertation

1. **Mezei, Z.**, Oláh, L., Kardos, L., Kovács, R.K., Csiba, L., Csépány, T.: Cerebrovascular hemodynamic changes in multiple sclerosis patients during head-up tilt table test: Effect of high-dose intravenous steroid treatment.
   J. Neurol. 260 (9), 2335-2342, 2013.
   DOI: http://dx.doi.org/10.1007/s00415-013-6977-0
   IF:3.841

2. **Mezei, Z.**, Bereczki, D., Rácz, L., Csiba, L., Csépány, T.: Can a physician predict the clinical response to first-line immunomodulatory treatment in relapsing-remitting multiple sclerosis?
   Neuropsychiatr. Dis. Treat. 8, 465-473, 2012.
   DOI: http://dx.doi.org/10.2147/NDT.S36771
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List of other publications

3. Csépány T., **Mezei Z.**, Csiba L.: Immunmoduláns kezeléssel szerzett tapasztalatok és ajánlások sclerosis multiplexben.
   Orvostud. Ért. 82 (2), 74-78, 2009.

4. **Mezei Z.**, Bereczki D., Csiba L., Csépány T.: A sclerosis multiplex funkcionális összetevő teszt alkalmazásának vizsgálata hosszú távon Debrecenben.
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   Ideggyogy. Szle. 58 (3-4), 113-118, 2005.

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