Long-term immunomodulatory treatment and quality of life of patients with multiple sclerosis

PhD Thesis

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List of abbreviations

GA – glatiramer acetate

HRQoL - Health related quality of life

IFNβ-1b - interferon beta-1b

IM – intramuscular

IMD – immunomodulatory drug

MS - multiple sclerosis

MSQoL-54 – Multiple sclerosis quality of life instrument

NAB - neutralising antibody

QoL – quality of life

RP - relapsing-progressive

RR - relapsing-remitting

SC – subcutaneous

SF-36 - short-form health survey

Original publications related to the PhD thesis

I. Bencsik, K., **Füvesi, J.**, Fricska-Nagy, Z., Rajda, C., Losonczi, E., Török, M., Vécsei, L.: Short communication: treatment of relapsing-remitting multiple sclerosis patients with IFN-beta1b: results of a 6-year follow-up. J Interferon Cytokine Res 2006; 26(2):96-100.
IF: 2.472

II. **Füvesi, J.**, Bencsik, K., Benedek, K., Mátyás, K., Mészáros, E., Rajda, C., Losonczi, E., Fricska-Nagy, Z., Vécsei, L.: Cross-cultural Adaptation and Validation of the „Multiple Sclerosis Quality of Life Instrument" in Hungarian. Mult Scler 2008; 14(3): 391-398.
IF: 3.312

III. **Füvesi, J.**, Bencsik, K., Losonczi, E., Fricska-Nagy, Z., Mátyás, K., Mészáros, E., Benedek, K., Rajda, C., Lencsés, G., Vécsei, L.: Factors influencing the health-related quality of life in Hungarian multiple sclerosis patients. J Neurol Sci 2010; 293(1-2): 59-64.
IF: 2.324 (2009)

Original publications connected to the PhD thesis

I. Bencsik, K., Rajda, C., **Füvesi, J.**, Klivényi, P., Járdánházy, T., Török, M., Vécsei, L.: The prevalence of multiple sclerosis, distribution of clinical forms of the disease and functional status of patients in Csongrád County, Hungary. Eur Neurol 2001; 46:206-209.
IF: 1.179

II. Bencsik, K., Rajda, C., **Füvesi, J.**, Járdánházy, T., Török, M., Vécsei, L.: Experiences with interferon-beta-1b treatment in MS after three year follow-up. (letter) Swiss Med Wkly 2002; 132:237.
IF: -

III. **Füvesi, J.**, Somlai, C., Németh, H., Varga, H., Kis, Z., Farkas, T., Károly, N., Dobszay, M., Penke B., Vécsei, L., Toldi, J.: Comparative study on the effects of kynurenic acid and glucosamine-kynurenic acid. Pharmacol Biochem Behav 2004; 77(1):95-102.
IF: 2.527

IV. Rajda, C., Bencsik, K., **Füvesi, J.**, Seres, E., Vécsei, L., Bergquist, J.: The norepinephrin level is decreased in the lymphocytes of long-term interferon-beta-treated multiple sclerosis patients. Mult Scler 2006; 12(3):265-70.
IF: 2.773

V. Fricska-Nagy, Z., Bencsik, K., Rajda, C., **Füvesi, J.**, Honti, V., Csépány, T., Dobos, E., Mátyás, K., Rózsa, C., Komoly, S., Vécsei, L.: Epidemiology of familial multiple sclerosis in Hungary. Mult Scler 2007; 13:260-261
IF: 3.26

VI. Bencsik, K., Fricska-Nagy, Z., Rajda, C., **Füvesi, J.**, Török, M., Vécsei, L., Csépány, T., Mátyás, K., Dobos, E., Rózsa, C., Semjén, J.: Effects of interrupted immunomodulant therapy on the neurological state of multiple sclerosis patients. (letter) J Neurol Sci 2007; 260(1-2): 296-297.
IF: -

VII. Losonczi, E., Bencsik, K., Fricska-Nagy, Z., Honti, V., Szalczer, E., Rajda, C., Illés, Z., Mátyás, K., Rózsa, C., Csépány, T., **Füvesi, J.**, Vécsei, L.: Tumour necrosis factor

alpha gene (TNF-alpha) -376 polymorphism in Hungarian patients with primary progressive multiple sclerosis. J Neuroimmunol 2009; 208(1-2): 115-8.
IF: 2.841

VIII. Losonczi, E., Bencsik, K., Fricska-Nagy, Z., Honti, V., Szalczer, E., Rajda, C., Illés, Z., Mátyás, K., Rózsa, C., Csépány, T., **Füvesi, J.**, Vécsei, L.: APOE epsilon status in Hungarian patients with primary progressive multiple sclerosis. Swiss Med Wkly. 2010 Nov 26; 140:w13119. doi: 10.4414/smw.2010.13119.
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Abstracts related to the PhD thesis

1. Bencsik, K., Rajda, C., **Füvesi, J**., Klivényi, P., Járdánházy, T., Török, M., Vécsei, L.: The prevalence of multiple sclerosis in Csongrád County, Hungary, Cephalalgia Hungarica, 1999. No.5., p.62, P-151.
2. Bencsik, K., Rajda, C., **Füvesi, J.**, Klivényi, P., Járdánházy, T., Török, M., Vécsei, L.: Experiences after 4-year follow-up of Interferon-beta-1b treatment: randomised, phase IV, open study, Journal of Neurology, 2001. Suppl.2. p.II./137., P-530.
3. Rajda, C., Bencsik, K., Fricska-Nagy, Z., **Füvesi, J.**, Török, M., Vécsei, L.: Six-year follow-up of relapsing-remitting multiple sclerosis patients with interferon-beta-1b treatment. Mult Scler 2003; 9:101.
4. Bencsik, K., Rajda, C., Csépány, T., Dobos, E., Mátyás, K., Fricska-Nagy, Z., **Füvesi, J.**, Török, M., Vécsei, L.: Prospective comparative phase IV clinical trial in multiple sclerosis patients treated with interferon-beta-1b or glatiramer acetate. Mult Scler 2003; 9.
5. **Füvesi, J.**, Bencsik, K., Mátyás, K., Mészáros, E., Rajda, C., Losonczi, E., Fricska-Nagy, Z., Török, M., Vécsei, L.: Quality of Life of Patients with Multiple Sclerosis in Hungary Based on the MSQOL-54 Instrument. Mult Scler 2004; 10. (Suppl 2) S132.
6. Mátyás, K., Bencsik, K., **Füvesi, J.**, Rajda, C., Fricska-Nagy, Z., Komoly, S., Vécsei, L. and the Hungarian study group: Six-year follow-up of relapsing-remitting multiple sclerosis patients with interferon-beta-1b treatment. Mult Scler 2004; 10. (Suppl 2) S246.
7. **Füvesi, J.**, Bencsik, K., Mátyás, K., Mészáros, E., Rajda, C., Losonczi, E., Fricska-Nagy, Z., Török, M., Vécsei, L.: Quality of life of 442 multiple sclerosis patients with different clinical forms in Hungary. J Neurol 2005; 252(Suppl 2.): 94.
8. **Füvesi, J.**, Hanrieder, J., Bencsik, K., Rajda, C., Kovács, K. S., Danielsson, R., Beniczky, S., Vécsei, L., Bergquist, J.: Differential neuroproteomics reveal characteristic protein expression changes in fulminant multiple sclerosis. Eur J Neurol 2008; 15(Suppl 3.):143-144.

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I. Introduction

Multiple sclerosis (MS), a demyelinative disorder of the central nervous system, affects mainly young adults in their most productive part of their life. Therefore it has a major impact on career planning, family life and social interactions. There are twice as many female as male patients. The first description of a case history that resembles the disease course of multiple sclerosis is written in the diary of an English aristocrat, Sir Augustus d'Esté, who lived in the first part of the nineteenth century (Landtblom et al., 2010). His disease started at the age of 28 with optic neuritis that soon recovered completely. Then he had diplopia, followed by paraparesis that lasted for three weeks, but gradually improved. Later he also suffered from imbalance, ataxia and incontinence. He could no longer go hunting or dance at balls and had to give up his career in the army, where he had been lieutenant colonel. Finally he was confined to wheelchair and died at the age of 54, decades before the disease was described by Charcot (Charcot, 1868).

The prevalence of multiple sclerosis in Hungary is 62/100,000, i.e. about 6000 Hungarians are affected by the disease (Bencsik et al., 2001). It is a chronic condition that has a great impact on quality of life.

I.1. Immunomodulatory treatment

There is still no curative therapy in MS. Until the middle of the 1990s, treatment of patients with the relapsing-remitting clinical form of the disease was restricted to treating the relapses with megadose parenteral corticosteroids. The first pharmacon with proved efficacy for the treatment of patients with the relapsing-remitting (RR) or relapsing-progressive (RP) forms of MS was interferon beta-1b (IFNβ-1b) (Betaferon) (Lublin and Reingold, 1996, Lublin et al., 1996). Early results (published in 1993) of a multi-centre, double-blind, placebo-controlled clinical trial proved that treatment with Betaferon was well tolerated and significantly reduced the activity of the disease and the number of active and new lesions detected by MRI in the relapsing-remitting form of MS (The IFNB Multiple Sclerosis Study Group, 1993, Paty and Li, 1993).

Currently available first-line immunomodulatory drugs (IMDs) are interferon beta-1a 30 ug weekly intramuscular injection, interferon beta-1a 44 ug subcutaneous (SC) injections 3 times weekly, interferon beta-1b 250 ug SC every other day and glatiramer acetate 20 mg

daily SC injection. In pivotal randomized placebo-controlled trials of IMDs reductions in relapse rates ranged from 18% to 34% and the treatment has been shown to slow the accumulation of lesion burden as determined by MRI (Jacobs et al., 1996, PRISMS Study Group, 1998, The IFNB Multiple Sclerosis Study Group, 1993, Simon et al., 1998, Rudick et al., 1999, Johnson et al., 1995). Because of the different study design, patient population and primary outcome measures it is difficult to compare these trials. Therefore prospective and randomized head-to-head trials were designed to assess the relative efficacy of different IMDs. These include "Independent comparison of interferons" (INCOMIN) trial (IFN beta-1b 250 ug SC every other day vs. IFN beta-1a 30 ug IM once weekly), "Evidence of Interferon Dose-response: European North American Comparative efficacy" (EVIDENCE) trial (IFN beta-1a 44 ug SC 3 times weekly vs. IFN beta-1a 30 ug IM once weekly, "Rebif vs Glatiramer Acetate in Relapsing MS Disease" (REGARD) trial (IFN beta-1a 44 ug SC 3 times weekly vs. GA 20 mg SC once daily) and "Betaseron/Betaferon Efficacy Yielding Outcomes of New Dose" (BEYOND) trial (IFN beta-1b 250 ug SC every other day, IFN beta-1b 500 ug SC every other day and GA 20 ug SC daily). While the higher dose, more frequently administered interferons were found to be more effective in the INCOMIN and EVIDENCE trials both regarding the clinical and MRI end-points, there was no significant difference between the treatment groups in the REGARD and the BEYOND studies (Durelli et al., 2002, Panitch et al., 2002, Mikol et al., 2008, O'Connor et al., 2009).

The effects of interferon-beta-1b on immunity in MS

The exact mechanism of IFN-beta in MS treatment is still unclear. IFN-beta-1b treatment induces the up-regulation of soluble vascular cell adhesion molecule (VCAM)-1, which correlates with the decrease in the number of Gd-enhancing MRI lesions (Calabresi et al., 1997). According to another study, IFN-beta-1b inhibits the adhesion of peripheral mononuclear cells to human cerebral endothelial cells (Corsini et al., 1997). Another proven mode of action is decreasing the activity of metalloproteinase (MMP-9) (Uhm et al., 1999, Corsini et al., 1999). MMP-9 takes part in the degradation of fibronectin, a major component of the basal membrane of cerebral endothelium. With the activities listed above, IFN-beta-1b decreases the migration and trafficking of lymphocytes into the central nervous system (CNS).

IFN-beta-1b induces IL-10 mRNA synthesis (Porrini et al., 1998). IL-10 inhibits the antigen-specific proliferation of Th1 clones and inhibits the synthesis of cytokines produced

by Th1 cells (IFNγ, TNFα and β, IL-1, IL-2 and IL-6). It has an immunostimulant effect on cytotoxic CD8+ cells.

Recently, it was demonstrated that the level of the proinflammatory cytokines osteopontin (OPN) and interleukin-17 (IL-17) are down-regulated by IFN-beta (Hong and Hutton, 2010). OPN is produces by Th1 cells and dendritic cells and its level was found to be elevated in the serum of MS patients. IL-17 is expressed by Th17 cells that seem to be important in the onset of MS.

Betaferon was approved for use in Hungary in 1996. Its long-term effects on the natural course of the disease can be evaluated on the basis of open studies.

I.2. Quality of life in MS

Health related quality of life (HRQoL) is a multi-dimensional construct that includes physical, mental and social health (Vickrey et al., 1995). There are three basic types of quality of life questionnaires: general, specific and combined, comprising of general health-related and disease-specific questions as well. General questionnaires are useful in primary care and in population-based studies with large number of cases. Specific questionnaires focus on the problems of a homogenous group of patients and are suitable for analysing HRQoL of patients with certain diseases. Combined instruments contain a general part and additional questions developed specifically for the study patients, therefore comparison of QoL of patients with different diseases and healthy subjects is possible.

General quality of life questionnaires: The Sickness Impact Profile was developed in the middle of the 1970s as a proposed outcome measure in evaluating health programs (Bergner et al., 1976). The MOS 36-Item Short-Form Health Survey (SF-36) was designed for use in clinical practice and research, health policy evaluations and general population surveys (Ware and Sherbourne, 1992, McHorney et al., 1993). The Duke-UNC Health Profile (DUHP) was developed to provide a quick assessment of health status for patients in primary care (Parkerson et al., 1981). The Functional Status Questionnaire (FSQ) is a brief, self-administered instrument for ambulatory patients (Jette et al., 1986). It describes patients' physical, psychological, social and role function. FSQ was also used to assess quality of life in multiple sclerosis and control patients in France, Germany and the United Kingdom in a cross sectional study (Murphy et al., 1998). The EuroQuol Group conducted postal surveys in England, The Netherlands and Sweden in the course of developing a standardised, non-

disease-specific instrument for valuing health states (The EuroQol Group, 1990). The aim of the study was the collection of a common data set for reference purposes.

Specific quality of life questionnaires: The Danish version of the Laman and Lankhorst Questionnaire (LLQ) (Laman and Lankhorst, 1994) was used to assess the effect of rehabilitation on the quality of life in patients with MS (Jonsson et al., 1996). The Multiple Sclerosis Impact Scale (MSIS-29) (Hobart et al., 2001) has been evaluated both in a community based sample and in three hospital based samples: in rehabilitation, during corticosteroid treatment and in primary progressive MS (Riazi et al., 2002). It has a high reliability and it is recommended for use as an outcome measure in different clinical settings. The Multiple Sclerosis International QOL questionnaire (MuSIQoL) has been developed in co-operation with neurologists, patients and health economists. It is a multidimensional self-administered instrument available in various languages in twenty countries (Simeoni et al., 2008).

Combined quality of life questionnaires: The Disability and Impact Profile (DIP) is a 2 x 39 item, self-administered questionnaire with parallel questions about disabilities and their impact on the patient, resulting in a profile of weighted scores (Lankhorst et al., 1996). Results in the MS group were compared with data from patients with rheumatoid arthritis and spinal cord lesion. Phennings et al. constructed a brief HRQoL questionnaire combining elements of the SF-36, COOP/WONCA Charts and the DIP (Pfennings et al., 1999). The new instrument was tested in a longitudinal study in MS patients. It adequately measures two dimensions of HRQoL, physical and psychological functioning.

The Multiple Sclerosis Quality of Life (MSQOL-54) Instrument is a combined questionnaire originally developed for English-speaking patients (Vickrey et al., 1995). It has two parts: general health-related questions of the SF-36 and 18 additional questions developed specifically to address problems of MS patients. The resulting 54 questions make up 14 scales, relating to Physical health, Role limitations due to physical problems, Role limitations due to emotional problems, Pain, Emotional well-being, Energy, Health perceptions, Social function, Cognitive function, Health distress, Overall quality of life, Sexual function, Satisfaction with sexual function, and Change in health. It is suitable for the measurement of QoL of MS patients, and using the general part it is possible to compare data with that of the general population (where it is available) or other patient groups. The instrument has been

validated (in chronological order) in Italian (Solari et al., 1999), French (Vernay et al., 2000), French Canadian (Acquadro et al., 2003), Japanese (Yamamoto et al., 2004), Spanish (Aymerich et al., 2006), Turkish (Idiman et al., 2006), Persian (Ghaem et al., 2007) and Serbian (Pekmezovic et al., 2007), reflecting that it is accepted and appreciated world-wide.

While a number of papers deal with clinical and demographic factors as predictors of the QoL in MS patients (Benito-Leon et al., 2002, Ayatollahi et al., 2007, Janardhan and Bakshi, 2002, Benedict et al., 2005, Patti et al., 2007, Lobentanz et al., 2004, Somerset et al., 2003, Miller and Dishon, 2006, Janssens et al., 2003), no data are available on the effects of different domains of QoL instruments and the predictive value of comorbid conditions on the QoL. Disease severity (EDSS), disease duration, cognitive function, depression and anxiety have been found to be related to the health-related quality of life (HRQOL) (Benito-Leon et al., 2002). When physical and mental (psychological) domains of the QoL were examined separately, the physical HRQoL was predicted by fatigue, depression and physical disability (EDSS), while the mental HRQoL was associated with depression and fatigue (Ayatollahi et al., 2007, Benedict et al., 2005). Lobentanz et al. found that a depressive mood is the main factor influencing the QoL (Lobentanz et al., 2004). The disability status, fatigue and reduced sleep quality impact mainly on the physical domains of the QoL. Depression and EDSS scores have been identified as the strongest predictors of the total 'Functional Assessment of Multiple Sclerosis' (FAMS), and almost all subscale scores (Patti et al., 2007).

II. Aims

The aims of our studies were to

1. examine the effects of long-term (6 years) interferon-beta 1b treatment on the relapse rate, progression index and EDSS score of relapsing remitting multiple sclerosis patients;
2. validate the MSQoL-54 instrument in Hungarian;
3. determine which factors influence the QoL of Hungarian MS patients (comorbid conditions, variables of the questionnaire having the biggest impact).

III. Patients and methods

III.1. Interferon-beta 1b

In 1996, we started to treat 34 relapsing-remitting and 2 relapsing-progressive MS patients with IFNβ-1b according to the guidelines of the American Academy of Neurology and the Hungarian Neurology Committee (Lublin et al., 1996, Report of the Quality Standards Subcommittee of the American Academy of Neurology, 1994). The inclusion criteria for treatment were (1) the relapsing-remitting or relapsing-progressive clinical form of the disease; (2) clinically and laboratory supported definite, or clinically supported definite MS according to Poser criteria (Poser et al., 1983); (3) an EDSS (expanded disability status scale) score of 0-5.5 (Kurtzke, 1983); (4) an age of: 18-50 years; and (5) at least 2 relapses in the last 2 years, or 1 relapse with fixed cerebellar symptoms.

The therapy was financed by the Hungarian Health Insurance Organization. From the 36 patients 28 received a continuous medication for six years. The demographic data on the patients are shown in Table 1.

Each patient underwent a neurological examination and the EDSS score was determined every 3rd month or in the event of a relapse. The laboratory parameters were checked every 3rd month in the first year, and twice a year later. We defined a sustained progression in disability as an EDSS change confirmed in two clinical examinations 3 months apart.

The primary end-point of this longitudinal follow-up study was the effect of 6 years of continuous IFNβ-1b treatment on the annual relapse rate. We compared the mean number of relapses in the 6th year of treatment with the mean number of relapses in the 2 years preceding treatment. The secondary end-point was the alteration in the progression index during the 6 years of treatment. To calculate this index, we divided the EDSS score of the patient by the duration of the disease. The tertiary end-point of the study was the change in the EDSS score of the patients as a result of the IFNβ-1b therapy. Finally we give the reasons of the drop-outs.

Statistical analysis of the data was performed with the non-parametric two-sample Wilcoxon test, with SPSS 11.0 statistical software.

III.2. Hungarian validation of the MSQoL-54 instrument

Translation Process

In the translation of the MSQOL-54 questionnaire we followed a similar method to that of the IQOLA project, which translated the SF-36 questionnaire into many languages (Bullinger et al., 1998, Ware and Gandek, 1998, Gandek and Ware, 1998). In brief, two independent forward translations of the original English questionnaire (both the SF-36 and the MS-specific module) were made by two translators, who are native speakers of Hungarian. Both translators are clinicians at the Department of Neurology, University of Szeged and they have an English-Hungarian Medical Translator Degree as well. Following a discussion on differences in translations and contemplating alternative expressions, a consensus forward translation was produced. The common forward-translation was given to a native speaker of British English who is fluent in Hungarian and was examined to be conceptually equivalent to the original English questionnaire. All members of the multiple sclerosis working group of the Department of Neurology took part in the cross-cultural adaptation process.

Data collection

The study was carried out at the Department of Neurology, University of Szeged in September and October 2003. Between January and April, 2004 two other centers joined our study: the Departments of Neurology at Markusovszky Hospital, Szombathely and Air Force Hospital, Kecskemét. We gave the questionnaires to consecutive multiple sclerosis patients attending the outpatient departments. The diagnosis of MS was made according to Poser criteria (Poser et al., 1983). Exacerbating patients were excluded. Cognitive function was not tested before administering the questionnaire. Patients either filled it out prior to the consultation with the neurologist, or took the questionnaire home and brought it back after completion. In Szeged most patients filled out the questionnaire at the out-patient unit. In the other two centers the questionnaire was given to patients by the neurologist during the consultation and they took it home. After the neurological examination the EDSS points were determined in case of each patient (Kurtzke, 1983). Data concerning the onset, the clinical form of the disease and the treatment medication was collected.

Ethics

Personal data of patients are kept confidential. All participating subjects were given information about the study both in a written form and personally. We obtained a written consent that their answers can be statistically evaluated. The study was approved by the Human Investigation Review Board of the University of Szeged, Albert Szent-Györgyi

Clinical Centre and it agrees with the Declaration of Helsinki. The same, ethically improved information sheet and approval form was given to participating patients at each centre.

Psychometric analyses

We created scale scores by transforming average scores to 0-100 possible scores, with higher values indicating better quality of life. Mean scale scores, standard deviations, percentages of respondents scoring minimum (floor) and maximum (ceiling) possible scores were calculated (Ware JE, 1993, Ware JE, 2000). Patient acceptability was assessed from mean time required to complete the questionnaire and percentage of missing answers on each scale. Internal consistency reliabilities were estimated for multiple item scales by calculating Cronbach´s alpha coefficient. Factor analysis was performed to examine the inter-relationship among the 12 MSQOL-54 scales. We evaluated construct validity by comparing patient groups known to differ on important clinical and demographic variables. We compared scale scores of patient groups defined by EDSS, duration of the disease, clinical forms of the disease, age and education.

Our hypotheses for construct validity were the following:

(Hypothesis 1) Patients with lower EDSS have higher HRQOL scale scores on all scales.

(Hypothesis 2) Patients with longer duration of the disease have worse quality of life.

(Hypothesis 3) Younger patients have better quality of life.

(Hypothesis 4) Clinical forms of the disease have an impact on HRQOL, 1st attack patients and those with benign clinical form of the disease having lower scale scores than patients with progressive forms of the disease.

(Hypothesis 5) We expected that the level of education does not affect scale scores of patients.

We compared our data to the original American study. We defined the level of significance at $p<0.05$ prior to processing the data. Statistical analysis was carried out with SPSS 11.0 statistical software.

III.3. Determinants of health-related quality of life in multiple sclerosis

The instrument

The Hungarian version of the MSQOL-54 instrument (Vickrey et al., 1995) was used. Analysis was carried out through the use of the data on the patients participating in the validation study.

Methods

We created scale scores by transforming average scores to possible scores in the range 0-100, with higher values indicating a better QoL.

We used question #53[1] and question #54[2] of the MSQOL-54 instrument to evaluate the overall QoL. We utilized regression analysis to determine which scale scores had the greatest impact on perceived QoL, as reflected by the answers to these two questions.

On the basis of the scores achieved, we divided patients into groups claiming to have a "very good", an "average" or a "very bad" QoL. We determined by logistic regression which variables contributed to predicting the probability of a patient belonging in a particular group.

The questionnaire was supplemented with a question asking the patients whether a physician had diagnosed them as currently having other medical conditions, in addition to MS, and to indicate such comorbid conditions among 21 listed (e.g. high blood pressure, diabetes, asthma, etc.). The same questions were used as in the original American study of the MSQOL-54 instrument by Vickrey et al. (Vickrey et al., 1995), but our patients were allowed to indicate other unlisted conditions. The answers of the patients concerning the number of comorbid conditions indicated, the most frequent comorbid conditions and whether they had an independent effect on the overall QoL were evaluated. The relationships between the comorbid conditions and the age, the disease duration, the clinical form of the disease and the level of education were also assessed.

Among the comorbid conditions, depression was dealt with independently. We hypothesized that MS patients with depression had a worse overall QoL, i.e. lower scores for questions #53 and #54, and that, besides the scales, depression was an independent factor determining the probability of belonging in the good or bad QoL group.

The cognitive function scale was examined in more detail. We assessed the mean cognitive function scores of the patients belonging in the different groups defined by the EDSS score, the disease duration, the age, the clinical form of the disease and the level of education.

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[1] Question #53 ("Overall, how would you rate your own quality of life", answers: 0-10, where 0=Worst possible quality-of-life; 10=Best possible quality of life)

[2] Question #54 ("Which best describes how you feel about your life as a whole?", answers: 1-7, where 1=Terrible, 2=Unhappy, 3=Mostly dissatisfied, 4=Mixed – about equally satisfied and dissatisfied, 5=Mostly satisfied, 6=Pleased, and 7=Delighted)

Statistical analyses

Prior to processing of the data, the level of significance was defined at $p<0.05$. Statistical analysis was carried out with the SPSS 15.0 statistical software.

IV. Results

IV.1. Interferon-beta 1b

Twenty-eight patients were treated continuously for 6 years, the clinical form of the disease in these patients remaining relapsing-remitting. As concerns the 8 drop-outs 2 patients interrupted the treatment only for the duration of their pregnancy and resumed it after giving birth. Although 1 patient died, the cause of death was unrelated to MS (perforated cholecystitis). One patient could not receive further IFNβ-1b therapy because of side-effects (permanent fever, flu-like symptoms and muscle pain) in the first 6 months of treatment. In 2 patients, the clinical form of the disease changed to secondary chronic progressive. Two patients were eliminated from the investigation because of the lack of compliance. The patients who continued and those who discontinued therapy did not differ significantly in terms of the demographic data. As regards the clinical data, the mean EDSS score of the drop-outs was higher at the beginning of therapy than that of the patients who continued therapy (Table 1). In the first 3 months of treatment, the typical side-effects described in the literature occurred in our patients. The laboratory parameters did not exhibit any changes due to the therapy.

	All patients	Continuously treated patients	Drop-outs
Number of patients	36	28	8
Male: female	1: 2.6	1: 3.7	1:3
Age (year) (mean±SD)	36.0±8.0	43.5±7.9	34.3±11.6
Duration of the disease (year) (mean±SD)	5.0±4.0	6.3±4.3	5.5±5.9
EDSS score (1996) (mean±SD)	2.0±1.2	1.8±1.2	2.9±1.7

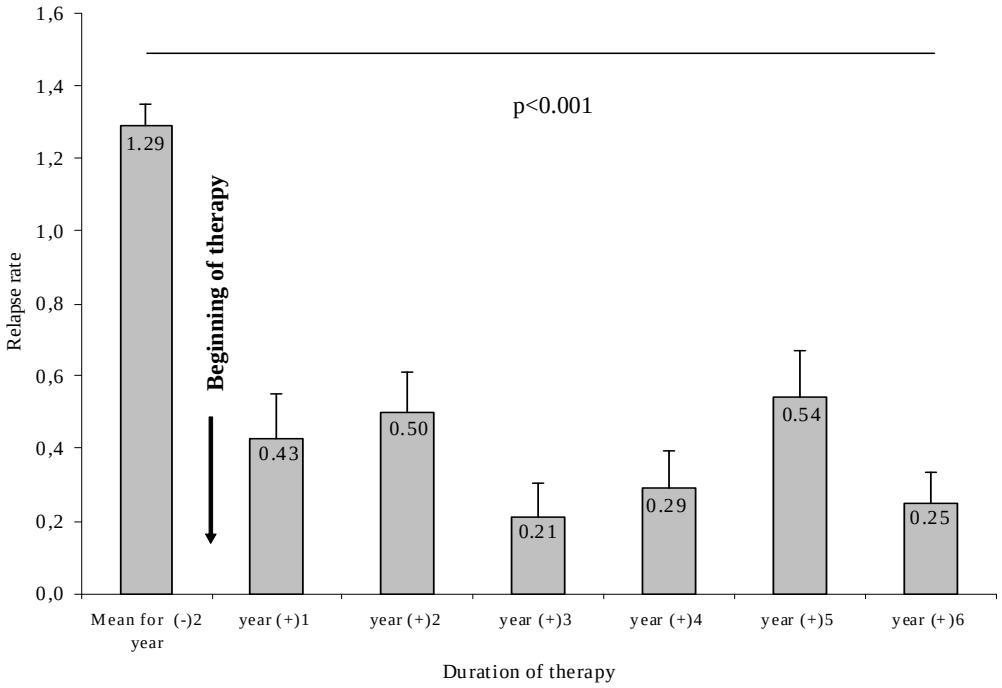
Table 1 Demographic data on the 36 patients at the beginning of the study, the 28 continuously treated patients and the drop-outs.

The mean annual relapse rate was 1.29±0.32 in the 2 years before the initiation of IFNβ-1b therapy. After 6 years of treatment, this rate decreased to 0.25±0.44, i.e. a decrease by 80.62% ($p<0.001$) (Figure 1), as a clear indicator that the clinical activity of the disease decreased significantly as a result of IFNβ-1b treatment.

The mean EDSS scores of the patients increased significantly during the period of treatment ($p=0.016$). At the commencement of therapy, the mean EDSS score of the patients was 1.77±1.19, while after 6 years of IFNβ-1b treatment it increased to 2.21 ± 1.48 (Figure 2).

The mean progression index (EDSS/duration of the disease) was 0.64±0.57 at the initiation of therapy, which by the end of the 6-year follow-up fell to 0.21±0.12, a significant decrease by 67.19% ($p<0.001$). Thus, IFNβ-1b treatment slowed the progression of the disease (Figure 3).

Figure 1 Effect of IFNβ-1b treatment on annual relapse rate (bars and numbers: mean; ┬: S.E.M.)



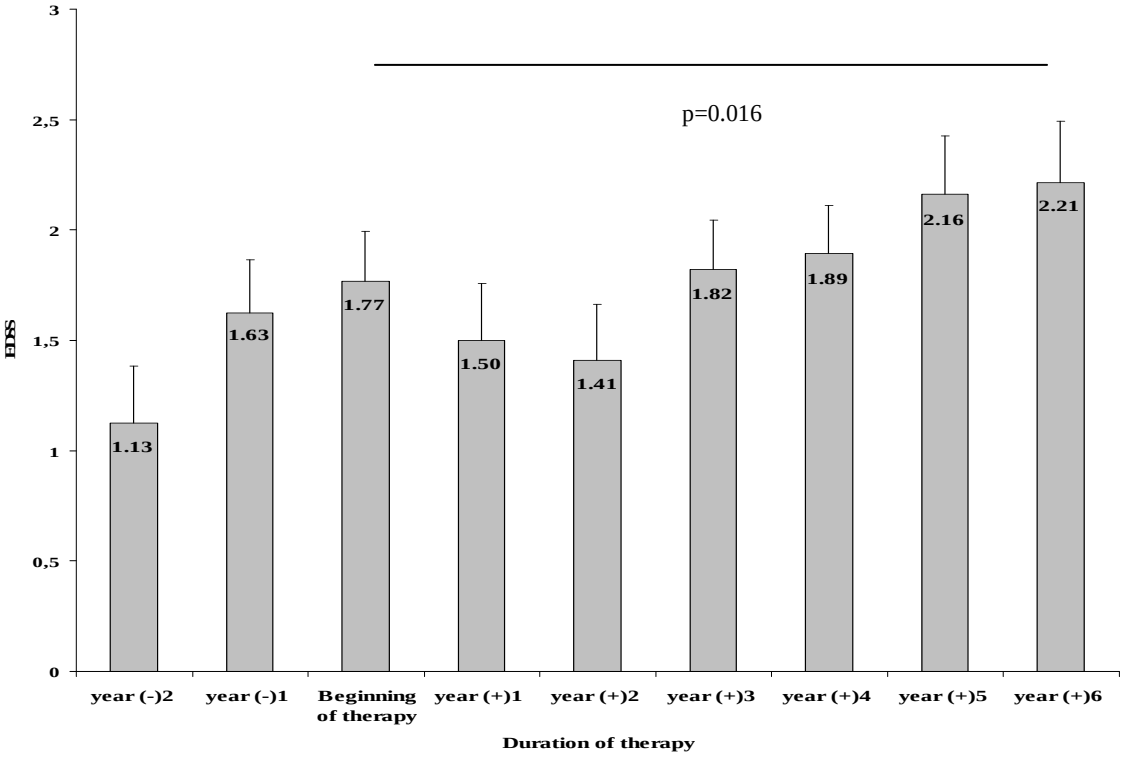


Figure 2 Change in mean EDSS score as a result of 6-year IFNβ-1b treatment (bars and numbers: mean; ┬: S.E.M.)

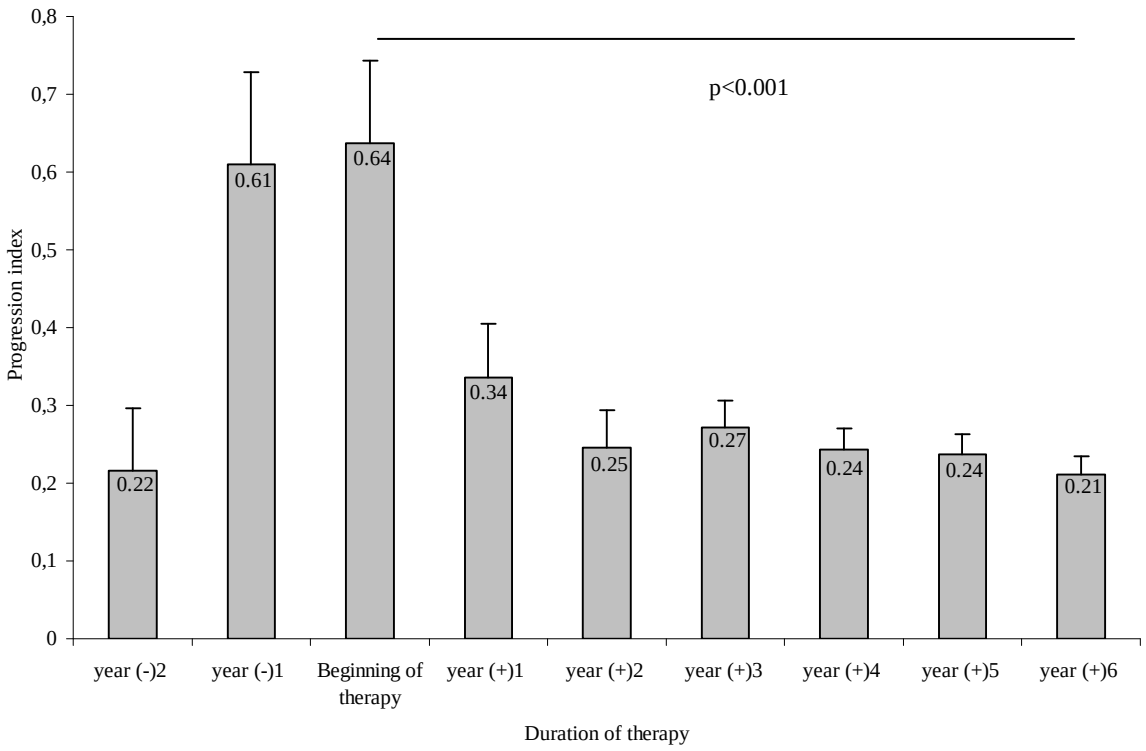


Figure 3 Change in progression index as a result of IFNβ-1b treatment (bars and numbers: mean; ┬: S.E.M.)

IV.2. Hungarian validation of the MSQoL-54 instrument

Cross-cultural adaptation findings

In general, finding appropriate phrases in translating the questionnaire was not difficult. However, we encountered some problematic questions due to cultural differences. We discussed changing the example “playing golf” in question 4, since it is not wide-spread at all in the general population. Finally we left it unchanged, since it is a well-known sport, even though not often played here. In case of question 9 (“Walking more than a mile”) the distance measurement “mile” had to be converted to kilometres, which is the used measurement in Hungary. We also altered the expression “walking one block/ several blocks” (question 10 and 11) to the more commonly used expression in this context: walking a distance of “one corner”. We also discussed in detail the translation of the possible response

choices before choosing the best alternative. The validated Hungarian version of the Multiple Sclerosis Quality of Life Instrument (MSQOL-54) is included in the Appendix of the thesis.

Demographic and clinical data

Altogether 438 patients filled out the questionnaire in the 3 MS centers. The demographic and clinical data of the patients in the three participating centers and altogether are summarised in Table 2 and 4.

Table 2 Demographic and clinical data of the patients

	Total	Szeged	Kecskemét	Szombathely
Number of patients	438	246	60	132
Age (year), mean ± SD (range)	43.3±11.1 (19-72)	41.7±10.8 (19-69)	43.8±10.9 (22-65)	46.1±11.3 (21-72)
ND (%)	15 (3.4)	7 (2.8)	2 (3.3)	6 (4.5)
Gender, women -n (%)	324 (74)	185 (75.2)	45 (75)	94 (71.2)
Education -n(%)				
primary	67 (15.6)	36 (14.6)	8 (13.3)	23 (17.4)
secondary	276 (64.2)	153 (62.2)	40 (66.7)	83 (62.9)
College, University	87 (20.2)	55 (22.4)	11 (18.3)	21 (15.9)
ND (%)	8 (1.8)	2 (0.8)	1 (1.7)	5 (3.8)
Clinical form of the disease				
1st attack	29 (6.6)	29 (11.8)	-	-
Benign	23 (5.3)	16 (6.5)	2 (3.3)	5 (3.8)
Relapsing-remitting	332 (75.8)	186 (75.6)	44 (73.3)	102 (77.3)
Sec. Chr. Progressive	35 (8.0)	5 (2.0)	9 (15.0)	21 (15.9)
Primary Progressive	9 (2.1)	4 (1.6)	1 (1.7)	4 (3.0)
ND (%)	10 (2.3)	6 (2.4)	4 (6.7)	-
Duration of the disease, year - mean±(range)	10.1±7.8 (0-43)	8.1±5.8 (0-29)	13.6±9.3 (1-42)	12.3±9.1 (1-43)
ND (%)	5 (1.1)	-	5 (8.3)	-
EDSS score -mean ± (range)	2.6±1.8 (0-9)	2.0±1.5 (0-9)	3.1±1.7 (0-8)	3.4±2.0 (0.5-8.5)
ND(%)	5 (1.1)	2 (0.8)	3 (5.0)	-

Scale scores

Mean scale scores counted on all patients range from 42.47±23.08 (mean±SD) on the scale “Health perceptions” to 75.88±24.75 (mean±SD) on the scale “Cognitive function”, only the scale score of “Sexual function” in the female group being higher than this, with an average score of 76.19±29.72 (Table 3).

Floor and ceiling effects

The highest percentage of respondents scoring minimum could be observed in case of the scales “Role-limitations- physical”, “Role-limitations- emotional” and “Satisfaction with sexual function”. The highest percentages scoring maximum were found on scales “Sexual function” (all patients, males and females as well), “Role-limitations –physical” and “Role-limitations- emotional” (Table 3).

Table 3 Descriptive statistics and reliabilities for MSQOL-54

Scale	n	No. of items	Mean	Standard deviation	Percentage scoring minimum	Percentage scoring maximum	Cronbach's alpha	Rate of missing answers N (%)
Physical function	408	10	56.26	31.45	4.8	10.3	0.953	30 (6.8)
Role-limitations- physical	426	4	44.06	41.33	37.7	26.7	0.861	12 (2.7)
Role-limitations- emotional	427	3	53.24	41.77	29.5	36.8	0.794	11 (2.5)
Pain	429	3	64.45	27.33	0.9	23.3	0.930	9 (2.1)
Emotional well-being	412	5	59.29	21.89	1.6	1.6	0.871	26 (5.9)
Energy	408	5	50.10	21.42	0.7	0.9	0.842	30 (6.8)
Health perceptions	422	5	42.47	23.08	0.7	0.5	0.801	16 (3.7)
Social function	422	3	65.53	26.62	1.6	16.2	0.801	16 (3.7)
Cognitive function	432	4	75.88	24.75	0.9	24.3	0.916	6 (1.4)
Health distress	430	4	52.94	29.41	6.4	4.1	0.934	8 (1.8)
Overall quality of life	425	2	59.39	18.01	0.5	0.0	0.832	13 (3.0)
Satisfaction with sexual function	393	1	59.16	32.86	13.7	24.4	---	45 (11.5)
Sexual function (all)	354	4	73.36	31.10	6.1	40.8	0.924	84 (19.2)
Male	109	4	65.77	33.49	8.0	28.6	0.908	5 (4.4)
Female	245	4	76.19	29.72	5.3	45.3	0.935	79 (24.4)
Change in health	437	1	46.62	21.45	3.4	6.2	---	1 (0.2)

Internal consistency reliability

Cronbach's alpha coefficients were over 0.8 in case of all scales except "Role-limitations- emotional" (0.794), indicating a good internal consistency reliability for group comparisons (Table 3).

Non-response, respondent burden

The highest rate of missing answers has been observed on scales "Satisfaction with sexual function", "Sexual function" (all patients) and "Sexual function" (females) (Table 2). The mean time required to complete the questionnaire was 24.36 ± 25.32 minutes (SD) and the median was 20.0 minutes.

Table 4 Description of groups for construct validity analysis

Groups	EDSS	%	Duration of the disease (year)	%	Age (year)	%
1	0-1.5	34.6	0-5	33.3	19-35	27.2
2	2-3	36.3	6-10	30.5	36-44	25.1
3	3.5-5	19.4	11-20	26.1	45-52	25.5
4	5.5< =	9.7	21< =	10.2	53< =	22.2

Construct validity

For the construct validity analysis we divided patients into groups with different EDSS points, duration of the disease, age, clinical form of the disease and education level as shown in Table 2 and 4 and compared mean scale scores of these groups. Results are summarised in Table 5. There was a significant difference between the EDSS groups on all scales. On each scale the patient group having lower EDSS score has better HRQOL scores (Hypothesis 1). We found a significant difference between patient groups with different duration of the disease on all scales except "Role-Emotional", "Mental Health" and "Cognitive Function". Patients with longer duration of the disease have worse quality of life, although the difference is not always apparent between groups 3 and 4 (Hypothesis 2). Considering age, a significant difference was observed between patient groups on all scales, younger patients having a better quality of life (Hypothesis 3). Comparing patient groups with different clinical forms of the disease there was a significant difference on all scales. First attack patients have a better QoL than patients with benign and relapsing-remitting clinical form, and patients with the

Table 5 Mean MSQOL-54 scale scores in patient groups defined by EDSS, duration of the disease, clinical forms of the disease, age and education

Scale	Physical function	Role-limitations-physical	Role-limitations-emotional	Pain	Emotional well-being	Energy	Health perceptions	Social function	Cognitive function	Health distress	Overall quality of life	Sexual function (all)	Satisfaction with sexual function	Change in health
EDSS														
0-1.5	79.93	64.89	63.56	76.18	65.55	60.18	54.86	80.33	81.92	65.50	68.71	82.95	67.91	55.70
2-3	57.26	38.64	47.44	60.51	55.04	43.78	39.00	64.36	70.91	51.77	57.72	73.32	61.21	46.82
3.5-5	34.28	31.55	53.97	56.06	60.54	47.90	35.45	55.85	75.96	45.96	54.29	66.52	50.00	38.69
5.5-	12.74	16.07	36.51	54.86	50.54	42.00	24.31	36.71	72.90	26.23	42.98	53.46	38.82	28.57
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Duration of the disease (year)														
0-5	69.67	54.80	58.16	69.74	60.23	55.26	47.89	70.89	76.70	58.29	62.65	76.77	64.18	51.57
6-10	58.04	45.83	53.79	63.87	59.58	49.05	43.62	67.08	76.55	53.54	60.40	77.69	60.54	47.16
11-20	44.73	32.37	48.53	60.47	57.99	45.83	37.27	61.50	74.51	48.45	56.05	66.01	52.23	42.26
21-	38.41	36.36	46.21	60.31	57.64	47.70	34.30	53.79	75.23	46.29	54.66	67.47	56.25	40.34
p	<0.001	<0.001	0.197	0.032	0.823	0.004	<0.001	0.001	0.892	0.022	0.008	0.010	0.044	0.001
Clinical forms														
1st attack	82.91	73.56	75.86	77.93	68.17	64.83	55.09	82.47	85.71	70.89	69.22	88.31	71.43	48.21
Benign	58.96	45.65	55.07	65.35	58.52	48.78	41.10	63.04	67.61	49.35	59.13	68.75	56.58	50.00
Primary Progressive	24.63	13.89	44.44	45.56	49.67	31.00	24.67	44.44	59.07	26.30	39.81	65.12	50.00	25.00
Relapsing-remitting	58.82	45.08	52.57	65.09	59.26	49.79	43.63	67.09	76.11	54.63	60.34	75.54	61.24	48.57
Sec. Chr. Progressive	14.64	14.29	31.43	48.84	52.23	43.37	24.29	38.69	76.00	28.29	45.05	44.70	33.59	28.57
p	<0.001	<0.001	0.001	<0.001	0.038	<0.001	<0.001	<0.001	0.025	<0.001	<0.001	<0.001	<0.001	<0.001
Age (year)														
19-35	77.11	64.35	67.25	77.19	64.87	56.96	53.53	78.15	83.35	62.52	67.91	85.60	70.98	52.63
36-44	57.03	48.43	55.40	67.39	61.27	50.67	44.18	70.36	75.97	56.95	60.87	75.42	60.75	49.29
45-52	51.18	33.72	48.61	57.36	56.16	45.65	37.61	60.80	70.61	48.88	55.48	70.04	56.57	45.37
53-	35.18	28.46	40.07	54.23	53.93	45.72	31.62	50.84	72.13	39.02	51.67	57.97	43.91	38.03
p	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Education														
primary	39.67	29.23	35.86	49.64	49.12	39.80	31.42	52.92	61.39	39.90	53.05	70.09	54.09	39.93
secondary	55.80	42.81	53.02	63.28	59.42	50.00	41.26	64.93	75.13	52.24	58.31	72.95	58.76	47.74
College, University	71.47	61.21	68.58	80.68	67.17	58.85	54.76	77.97	89.02	65.86	67.80	77.91	63.72	49.13
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.284	0.235	0.014

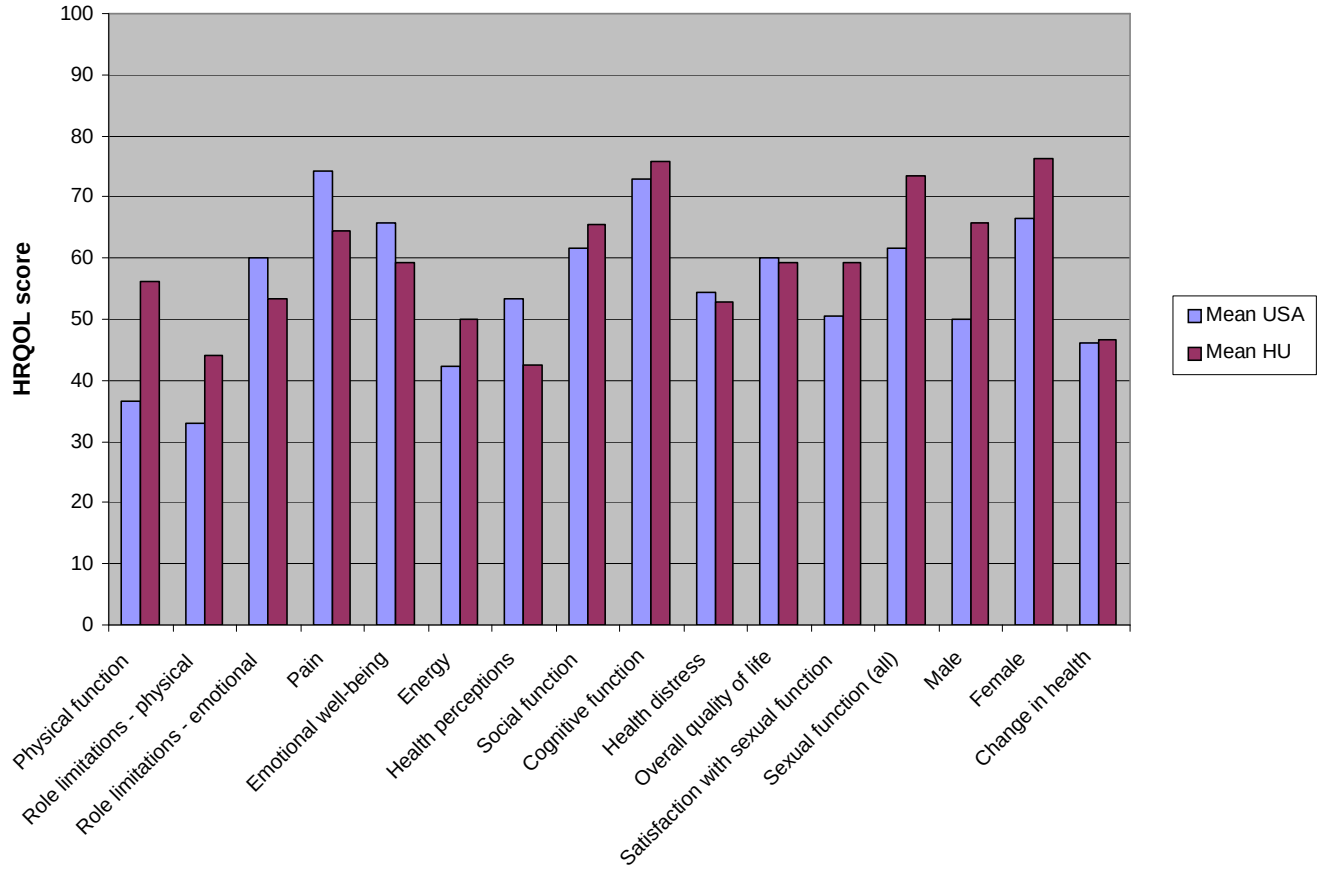
progressive forms of the disease have the worst QoL (Hypothesis 4). Patients with different education levels had significantly different scores on all scales except “Sexual function” and “Satisfaction with sexual function”. Patients who have higher education have better quality of life (Hypothesis 5). Our hypotheses were verified except hypothesis 5.

Comparing our results to the data of the original American study, we found some significant differences between the mean scale scores of the two patient groups (Table 6 and Figure 4). Mean scale scores of the American sample were higher on scales “Pain”, “Emotional well-being” and “Health-perceptions”. Mean scale scores of the Hungarian sample were higher on scales “Physical function”, “Role-limitation – physical”, “Energy” and on scales dealing with sexual function. There were no significant differences regarding the other scales, including “Overall quality of life”.

Table 6 Comparison of mean scale scores of the American and the Hungarian multiple sclerosis patient samples

Scale	HU N	HU Mean	HU Sd	US N	US Mean	US Sd	t stat	t prob
Physical function	408	56.26	31.45	178	36.7	32.5	6.85	*0.000
Role-limitations- physical	426	44.06	41.33	173	32.9	39.0	3.04	*0.002
Role-limitations- emotional	427	53.24	41.77	173	60.0	42.3	-1.79	0.074
Pain	429	64.45	27.33	179	74.2	25.5	-4.09	*0.000
Emotional well-being	412	59.29	21.89	177	65.6	20.4	-3.27	*0.001
Energy	408	50.10	21.42	179	42.2	20.9	4.14	*0.000
Health perceptions	422	42.47	23.08	85	53.3	25.3	-3.88	*0.000
Social function	422	65.53	26.62	179	61.7	25.0	1.64	0.101
Cognitive function	432	75.88	24.75	177	73.0	24.2	1.31	0.190
Health distress	430	52.94	29.41	176	54.4	26.9	-0.57	0.570
Overall quality of life	425	59.39	18.01	179	60.1	20.1	-0.43	0.669
Satisfaction with sexual function	393	59.16	32.86	150	50.5	38.3	2.62	*0.009
Sexual function (all)	354	73.36	31.10	160	61.7	35.4	3.77	*0.000
Male	109	65.77	33.49	46	49.9	34.5	2.67	*0.008
Female	245	76.19	29.72	114	66.4	34.7	2.75	*0.006
Change in health	437	46.62	21.45	179	46.1	25.7	0.26	0.797

Figure 4 Comparison of mean scale scores of the American and the Hungarian multiple sclerosis patient samples



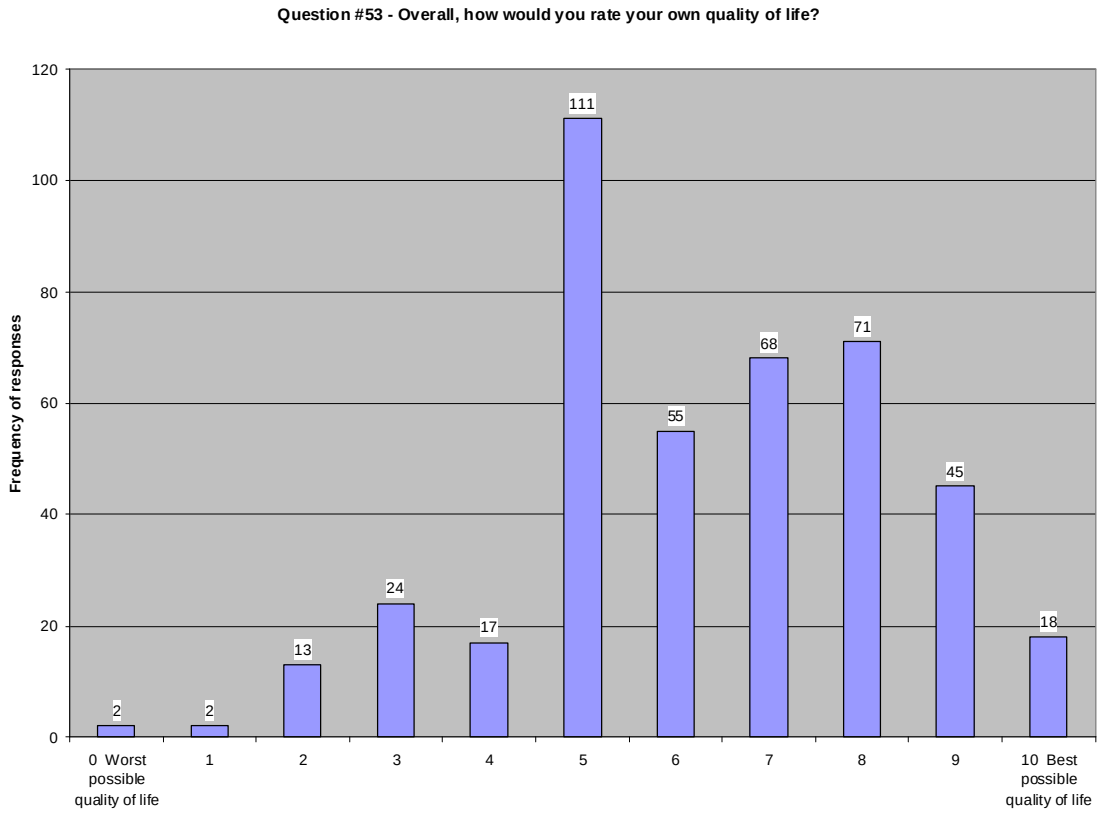
IV.3. Determinants of health-related quality of life in multiple sclerosis

Overall quality of life

Figure 5 shows the frequencies of the responses given by the patients to questions #53 and 54 of the instrument. Most patients reported a good QoL. In the responses to question #54 no patients indicated the answer “delighted”, which reflected the best QoL on this scale.

Factors influencing overall quality of life

As regards question #53 the **social function**, **general health**, physical function, **mental health**, and **satisfaction with sexual function** scale scores had the greatest influence on the overall QoL ratings. For question #54, the **mental health**, **general health**, **satisfaction with sexual function**, reported health transition, **social function** and pain scale scores had the



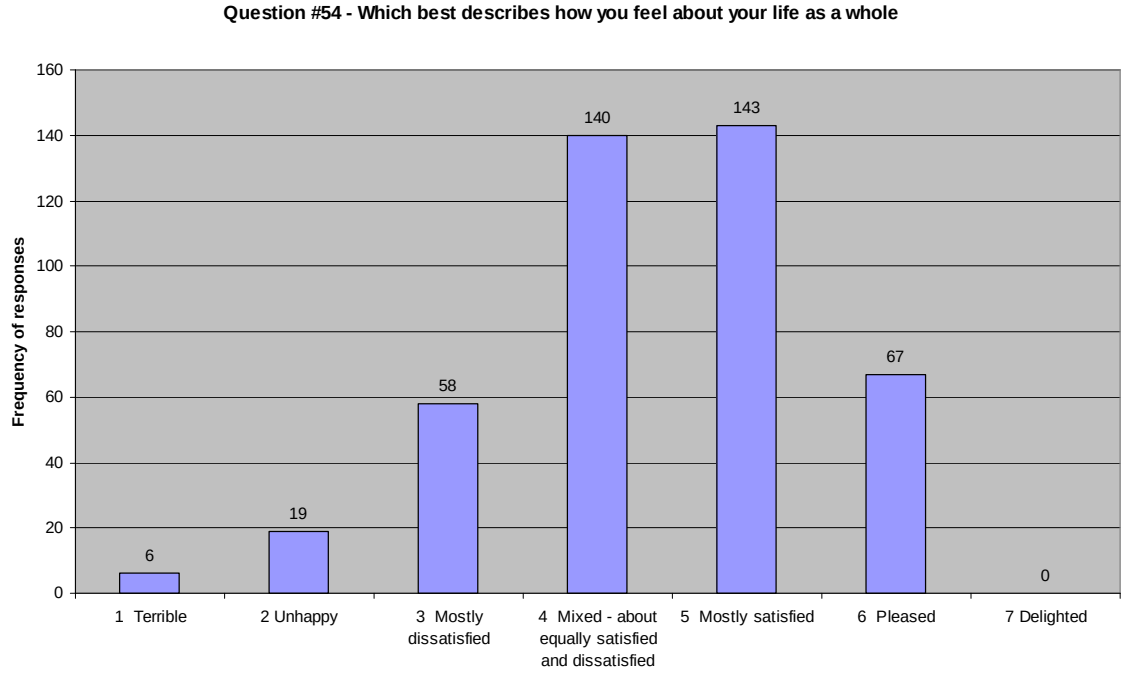


Figure 5 Overall quality of life

most appreciable impact on the perceived QoL. Four of the variables (indicated in bold) featured as the most decisive scales in the model in both cases, confirming the result (Table 7).

Table 8 summarizes the scales predicting the probabilities of a patient to belonging in the group with the best or the worst QoL. The **mental health, general health, satisfaction with sexual function** and physical function scales appeared most frequently.

Comorbid conditions

272 patients (62.1%) indicated that, besides MS, they had another medical condition diagnosed by a physician (Table 9). Most patients reported only 1 or 2 such medical conditions, but the highest number was 8. The 10 medical conditions reported most frequently by the patients are listed in Table 10. Constipation, the most commonly featuring comorbid condition, may in fact be a vegetative symptom of MS, and therefore should not be considered an independent condition. Anaemia may be associated with the use of medications, and accordingly this is not a real comorbid condition either.

Table 7 Scales with the highest impact on the overall quality of life measured via questions #53 and #54

Question #53 ("Overall, how would you rate your own quality of life")	**β**	**t**	**p**	**Question #54 ("Which best describes how you feel about your life as a whole?")**	**β**	**t**	**p**
1. General health	0.267	5.913	**<0.0001**	1. Mental health	0.349	7.659	**<0.0001**
2. Physical function	0.265	5.426	**<0.0001**	2. General health	0.246	5.195	**<0.0001**
3. Mental health	0.218	5.043	**<0.0001**	3. Satisfaction with sexual function	0.209	5.212	**<0.0001**
4. Satisfaction with sexual function	0.130	3.385	**0.001**	4. Social function	0.150	2.793	**0.005**
5. Social function	0.109	1.956	**0.051**	5. Reported health transition	0.102	2.636	**0.009**
				6. Pain	-0.106	-2.365	**0.019**

Table 8 Summary of scales predicting the probabilities of a patient belonging in the groups with the best or the worst quality of life

Question #53					
Very bad	*Exp (B)*	*p*	*Very good*	*Exp (B)*	*p*
physical function	0.972	0.043	physical function	1.039	0.006
mental health	0.946	0.002	mental health	1.041	0.042
health distress	1.031	0.017	general health	1.048	0.001
health transition	0.966	0.019	satisfaction with sexual function	1.027	0.011
Question #54					
Dissatisfied	*Exp (B)*	*p*	*Satisfied*	*Exp (B)*	*p*
body pain	1.027	0.003	mental health	1.052	0.004
mental health	0.932	<0.0001	general health	1.030	0.010
general health	0.964	0.015	satisfaction with sexual function	1.022	0.022
sexual function	0.977	0.048			
satisfaction with sexual function	0.975	0.005			
health transition	0.978	0.045			

Exp (B) indicates how an increase in the given variable by one changes the probability of a patient falling into a specific category of the dependent variable.

Table 9 Comorbid conditions

No. of comorbid conditions	N	Percentage	Cumulative percentage
0	166	38	38
1	120	27	65
2	80	18	83
3	28	6	89
4	20	5	94
5	12	3	97
6	7	2	99
7	3	0.5	99.5
8	2	0.5	100
Total	438	100	

Table 10 The 10 most frequent comorbid conditions

	Comorbid condition	Responses	Percentage of patients (n=438)
1.	constipation	92	21
2.	depression	89	20.3
3.	high blood pressure	60	13.7
4.	leg cramps while walking	54	12.3
5.	varicose veins	52	11.9
6.	arthritis	51	11.6
7.	sinus congestion	26	5.9
8.	hip impairments	21	4.8
9.	hearing difficulty	18	4.1
10.	anaemia	17	3.9

Depression

Depression was indicated by 89 patients, i.e. 20.3% of all the respondents. Most of the patients with depression had an EDSS of 2-3 points, a disease duration of 5 or less years and had a secondary education level, and exhibited the relapsing-remitting clinical form. The age distribution did not seem to be specific.

The responses to both questions #53 and #54 revealed that the depressed patients had a significantly worse QoL ($p<0.0001$ in both t-tests) (Figure 6). On the other hand, when depression was examined together with all the scale scores, it was not among the variables that played the major role in determining the overall QoL.

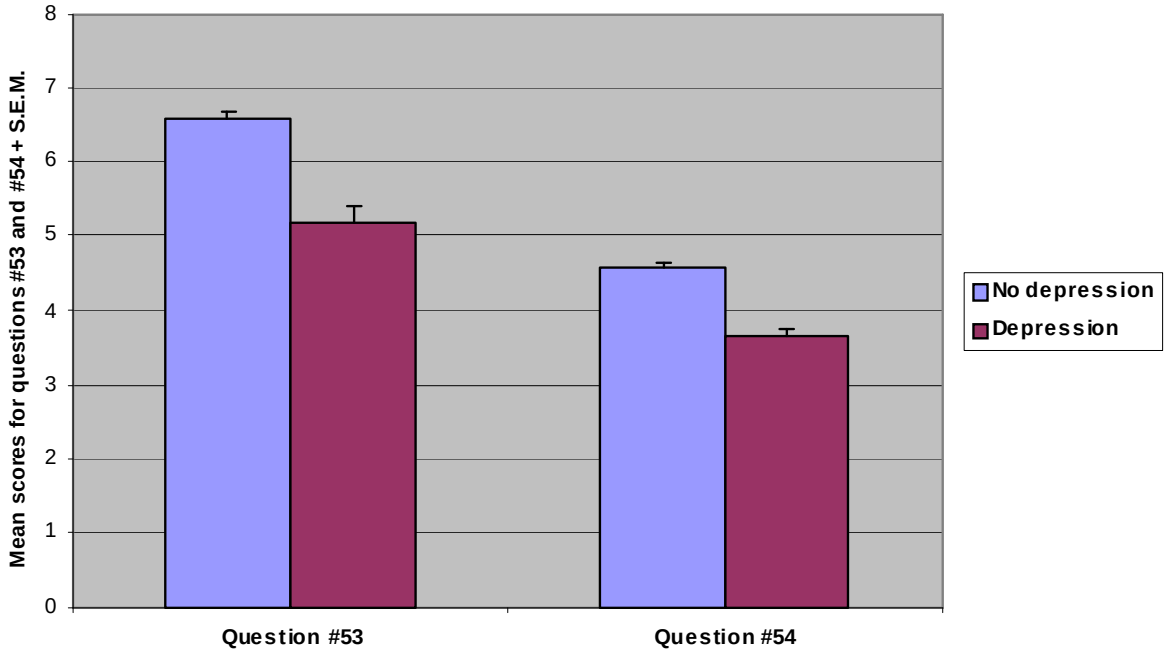
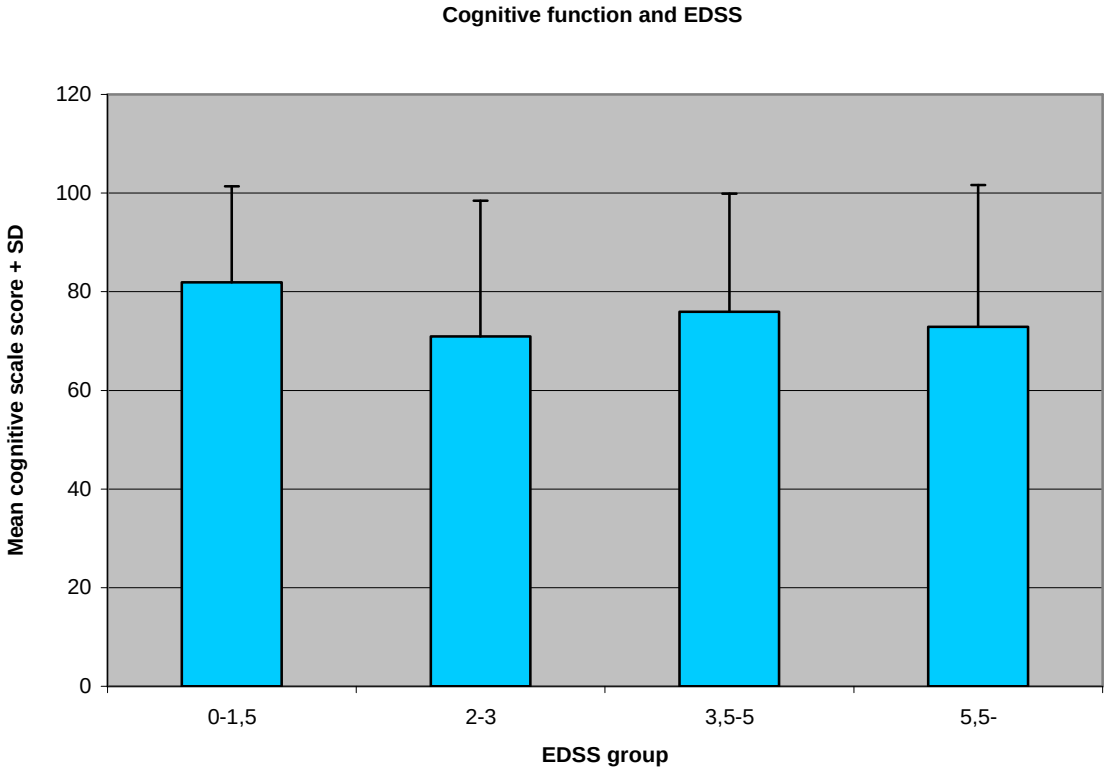


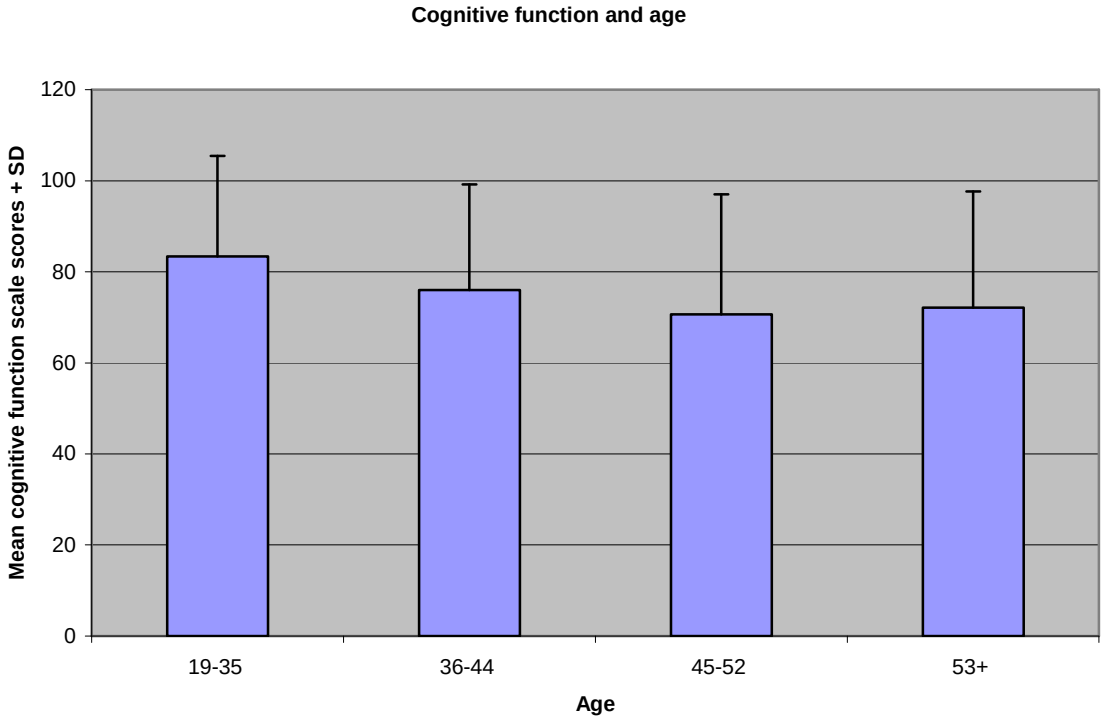
Figure 6 Depression and quality of life

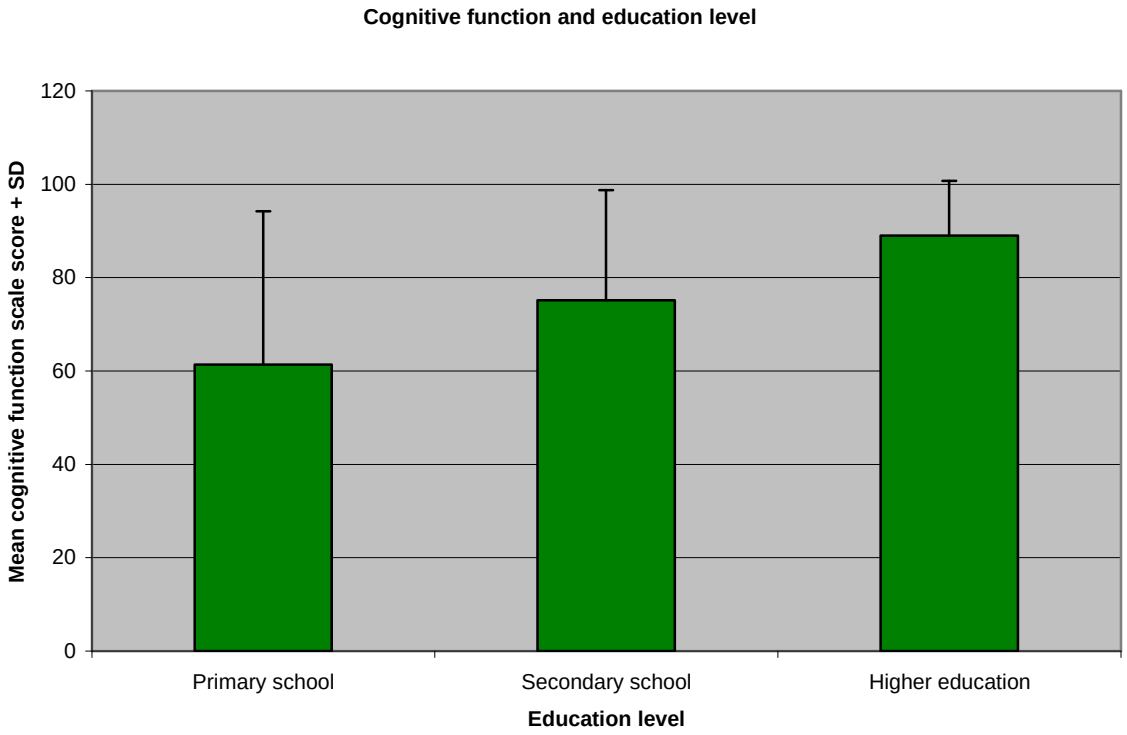
Cognitive function

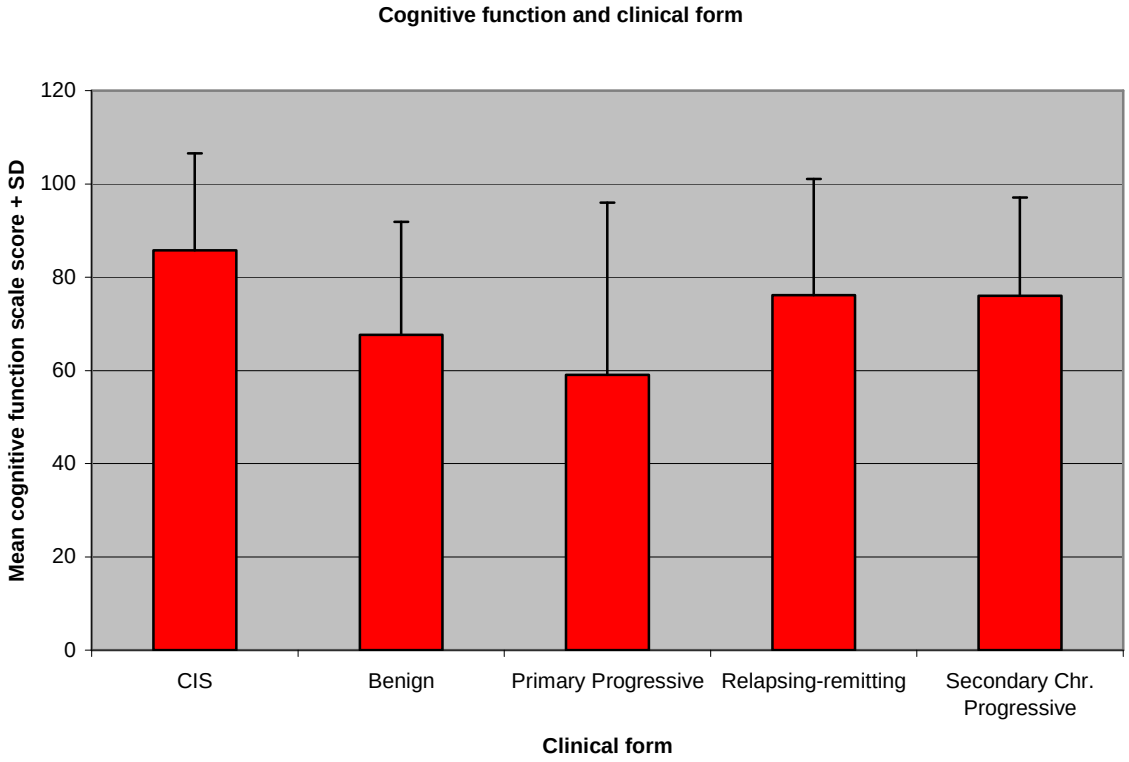
There were significant relationships between the cognitive function scale score and the EDSS, age, education and clinical form, but not the duration of the disease (Figure 7; for comparison the patient groups are described in Table 4). Young patients, patients with a low EDSS score, and patients with a high level of education had a better cognitive function. As concerns the clinical forms of the disease, CIS (Clinically isolated syndrome) patients scored much higher than the others on the cognitive function scale, indicating only a mild cognitive deficit. The relapsing-remitting and secondary progressive patients had fewer cognitive problems than the patients with the benign or primary progressive clinical form.

Figure 7 Cognitive function in patient groups defined by EDSS, clinical form, age and level of education.






Cognitive function and education level
Mean cognitive function scale score + SD
120
100
80
60
40
20
0
Primary school
Secondary school
Higher education
Education level


Cognitive function and clinical form
Mean cognitive function scale score + SD
120
100
80
60
40
20
0
CIS
Benign
Primary Progressive
Relapsing-remitting
Secondary Chr. Progressive
Clinical form

V. Discussion

V.1. Interferon-beta 1b

The observed 80% decrease in the relapse rate of IFNβ-1b-treated MS patients in our open study is not in line with the 18-34% change reported from multi-centre, double-blind, placebo-controlled clinical trials (The IFNB Multiple Sclerosis Study Group, 1993, Jacobs et al., 1996, PRISMS Study Group, 1998).

In similar open studies lasting for 1-3 years, a 50-86% decrease in relapse rate was experienced (Arbizu et al., 2000, Carra et al., 2003, Onesti et al., 2003, Milanese et al., 2003, Huber et al., 1996, Khan et al., 2001, Dubois et al., 2003). During this period, a significant change in the EDSS score of the patients was not found. In 2000, Johnson et al. published the results of a 6-year course of treatment with glatiramer acetate (Copaxone) (Johnson et al., 2000). The initial mean annual relapse rate of 1.50 decreased to 0.42 by the end of the 6^{th} year, i.e. a 72% change. An unchanged status or an improvement in the EDSS score of at least 1 point was observed in 69.3% of the patients, a finding similar to ours.

Multiple sclerosis registry studies show an average survival time of MS patients ranging from 20 to 45 years from the onset of disease symptoms (Bronnum-Hansen et al., 2004, Sumelahti et al., 2010, Smestad et al., 2009, Wallin et al., 2000, Hirst et al., 2008, Leray et al., 2007). However, there is a significant negative impact on life expectancy due to MS, the survival disadvantage ranging from 7 to 14 years compared to the general population. The longest follow-up study of IFNβ-1b treatment was carried out by Ebers et al (Ebers et al., 2009, Ebers et al., 2010, Reder, 2010). The results of the 16 and 21 year long-term follow-up of the original Betaferon pivotal trial showed that early and sustained therapy is associated with marked reductions in the risk of reaching substantial disability milestones (e.g. reaching EDSS 6 or developing SPMS). Moreover, an increased death rate was observed among those originally randomized to placebo compared to those originally randomized to IFN beta-1b. Patients treated earlier with Betaferon had a 39.3% relative reduced risk in mortality for the time since randomization in the study (p=0.027), compared with patients receiving placebo for the first five years of treatment. Eight patients needed to receive early Betaferon treatment in the trial (number needed to treat) in order to avoid one death, as compared to placebo. The positive effect of interferon beta-1b on survival needs to be further examined, but this information may be beneficial in the every-day patient management to improve adherence to therapy.

The significance of our present study lies in the long-term, prospective follow-up of the patients. This refers to the drop-outs as well. The weaknesses of the study are the lack of MRI data and neutralising antibody (NAB) evaluation, the small number of patients and the fact that it is not a blind-controlled trial. The initial diagnostic MRI and treatment of the patients was financed by the National Health Insurance Organization. However, further MRI follow-up was not financed at the time of the study. In long-term studies, a placebo control is not allowed for ethical reasons.

Since the time of our study, guidelines have been published concerning the use of anti-IFN-beta antibody measurements and the role of data on NAB in clinical practice (Sorensen et al., 2005, Polman et al., 2010). Clinical, MRI and NAB data have to be taken into account when making therapeutic decisions. New aspects of the latest recommendations are that (1) even patients with a good therapeutic response to IFN-beta should be tested and (2) that in cases of sustained high-titre NAB positivity, a switch to a non-interferon-beta treatment should be considered (Polman et al., 2010). Therapy should be switched irrespective of NAB in patients whose disease activity is not controlled effectively.

The less than 0.5 point increase in the EDSS score contrasts markedly with the 3-point deterioration expected after 6 years according to the natural disease course. Moreover, the mean EDSS score at the end of the therapy (2.21±1.48) is lower than the 4-5 points to be expected after a 10-12-year history of MS (Ebers, 2001).

The significant improvement in the progression index demonstrates that 6 years of continuous therapy decreased the progression of the disease, i.e. IFNβ-1b treatment stabilizes the status of the patients.

V.2. MSQOL-54 - Hungarian validation

The Hungarian version of the MSQOL-54 was accepted well by patients with multiple sclerosis. None of the patients refused to fill it in. The average time needed to complete it was 24 minutes (median 20 minutes), which means that it was not a difficult task for the patients and that the wording of the questionnaire was easy to understand. In other studies the average time to complete the MSQOL-54 ranged between 11.8-30.0 minutes (Idiman et al., 2006, Solari et al., 1999, Acquadro et al., 2003, Aymerich et al., 2006).

Regarding the ratio of missing answers we found similar results to other authors (Vickrey et al., 1995, Solari et al., 1999, Idiman et al., 2006). The rate of missing answers was less than 7% in case of all scales except those addressing sexual function and satisfaction with

sexual function. The exceptionally high rate of missing answers on the sexual function scale (19.2%) is mainly caused by the fact that 24.4% of females did not answer this question. The same number for male responders was only 4.4%. This phenomenon may be due to cultural reasons: it is still not easy for patients, especially women to speak openly about these issues even with health personnel. The mean scores on these scales are also interesting, because these are relatively high compared to other mean scale scores indicating that patients did not have problems with sexual function. On the other hand, sexual dysfunction is present in 57.0-77.4% of multiple sclerosis patients according to the literature (Mattson et al., 1995, Zivadinov et al., 2003). We can conclude that this is the most problematic part of the questionnaire and it has to be further improved. This is supported by the fact that a low response rate was found on these scales in Italy, Turkey and in the original American study as well. In fact, one initiative was made by Solari et al., who added an additional response "not applicable" to one sexual function item and to the sexual satisfaction item in their longitudinal survey assessing changes in self-reported HRQOL over 5 years in MS patients (Solari et al., 2006). With this modification they managed to improve response rate on these scales, while the proportions of missing answers for the other domains were similar to those found in their first study.

We found that the patient group having lower EDSS score had better HRQOL scores on each scale. In the Turkish validation study authors found a weak negative correlation between EDSS and both physical and mental health composite (Idiman et al., 2006). However, the correlation was significant in the lower EDSS group (EDDSS 0-4.0). Since more than 90% of our patients had an EDSS score below 5.5, this shift to lower level of disability may influence our results as well. When comparing groups of patients with different ambulation status Vickrey et al. found that the sensitivity of scales assessing aspects of ambulation was higher to the known group differences than scales assessing well-being or cognition (Vickrey et al., 1995). There was a non-linear relationship between ambulation status and HRQOL for some scales, for example pain. In the Italian validation study neurological impairment assessed by EDSS had a limited influence on quality of life measured by MSQOL-54 (Solari et al., 1999). However, the mean EDSS in their patient sample was much higher than that of both our and the Turkish study.

Younger patients with a higher level of education, shorter duration of the disease and a 1st attack or benign clinical form of the disease had a better quality of life. Of these parameters the effect of the level of education is not so evident to understand. Its beneficial influence on perceived quality of life might be due to the fact, that highly educated patients

manage to remain employed for a longer time despite of accumulation of physical disability or have better chances to find another job more suitable to their changed capabilities.

Comparing the self-assessed quality of life of the Hungarian and the American multiple sclerosis patient samples we found significant differences between some of the mean scale scores. The two samples were similar considering mean age, sex distribution and mean duration of the disease. On the other hand, in the American sample the proportion of patients capable to walk without aid (EDSS<=5.5) was only 41%, compared to more than 90% in our sample. The other difference was that more patients had a college or university degree in the American than in the Hungarian sample (Vickrey et al., 1995). The lower mean EDSS score of the Hungarian patient group may account for the higher mean scores on scales assessing mainly physical function and energy. There were no significant differences in the mean scores of scales less sensitive to ambulation such as “Cognitive function” or “Role-limitation – emotional”.

Possible limitations of our study are first that we did not test the cognitive function of patients before administering the questionnaire. This may influence the quality of the data collected. However, Gold et al. showed that cognitive impairment in multiple sclerosis does not affect reliability and validity of self-report health measures (Gold et al., 2003). Second, some validity aspects, such as test-retest reliability were not assessed.

V.3 Factors influencing health-related quality of life

Factors influencing the overall QoL: Three of the scales that determine whether a patient falls in the best or the worse QoL category are those with the highest impact on the overall QoL (mental health, general health and satisfaction with sexual function scales). Interestingly, the physical function scale does not feature among them.

62.1% of the patients indicated having at least one comorbid condition besides MS. We examined the effects of *depression* in more detail.

The prevalence of depression among MS patients has been reported to be 36-54% (Fruehwald et al., 2001, Joffe et al., 1987, Sadovnick et al., 1996). Joffe et al. (Joffe et al., 1987) found that 13% of their MS patients had a bipolar affective disorder as opposed to 1% in the general population. There was no direct relationship between the degree of functional disability and the clinical disorders of mood. A highly significant correlation was found between depression, anxiety and the QoL (Fruehwald et al., 2001). Depression was the strongest predictor of a reduced QoL. The study by Sadovnick et al. (Sadovnick et al., 1996)

concluded that MS patients had a 50.3% lifetime risk of depression. Among first-degree relatives of index cases, the morbidity risk for depression was lower than that among the reference population.

For our MS patients, the reported rate of depression was relatively low: only 20.3% of the subjects indicated a current diagnosis of depression. We considered patients as having depression whose diagnosis had been confirmed by a psychiatrist. A recent study led to the finding that the prevalence of major depression in primary care practices in Hungary was 7.3% (Peter et al., 2008). The rate of depression is higher in the MS patient population relative to patients visiting primary care practices. Patients with depression scored significantly lower on both scales for assessment of the overall QoL. In the study by Vickrey et al. (Vickrey et al., 1995), the scores of the depressed patients (15/179) were significantly lower than those of the non-depressed subjects on all scales except those relating to physical function and cognitive function. In an Italian survey too (Solari et al., 1999), depression had a major influence on the HRQOL. Patients with higher BDI (Beck Depression Inventory) scores displayed lower scores on all MSQOL-54 scales. This finding is in accordance with the results of another Italian study (Patti et al., 2003). Janardhan et al. (Janardhan and Bakshi, 2002) assessed the QoL of 60 consecutive MS patients with the MSQOL-54 instrument. After disability and fatigue had been taken into account, depression proved to be associated with a lower QoL in many domains.

The prevalence of a *cognitive impairment* among patients with multiple sclerosis has been variously reported in the range 30-70% (Bobholz and Rao, 2003, Pal et al., 2002, Piras et al., 2003, Sfagos et al., 2003). This high rate makes it necessary to pay attention to this aspect. The reported dysfunctions involved attention, recent memory, information processing speed, executive functions, verbal intellectual ability, visuospatial perception, abstract reasoning and verbal memory (Bobholz and Rao, 2003). Cognitive deficits seem to develop as early as one year after the onset of MS and subsequently remain comparatively stable, without rapid worsening (Piras et al., 2003). The accumulating physical disability makes it more complicated to execute certain tasks included in the tests measuring cognitive functions. Electrophysiological studies of visual and auditory event-related potentials are therefore very important for the evaluation of the cognitive status (Piras et al., 2003, Sfagos et al., 2003). Complex MRI and neuropsychological studies (Bobholz and Rao, 2003, Pal et al., 2002, Piras et al., 2003) have indicated that cognitive deficits correlate with MRI lesions of specific brain

regions rather than the overall MRI lesions. One study demonstrated that the Kurtzke scale, atrophy of the corpus callosum and widening of the third ventricle and Sylvian fissures were related to an impaired cognitive performance (Pal et al., 2002). Multiple sclerosis patients performed worse in verbal and non-verbal theory of mind (ToM) tasks, indicating that social cognition, especially emotional recognition is affected in MS (Banati et al., 2010). More disabled patients and patients with long disease duration had worse results. Moreover, ToM was found to be more impaired in case of rapid disease progression.

In our study, young patients, patients with a low EDSS scores, and patients with a high level of education had a better cognitive function. CIS patients gave higher scores on the cognitive function scale than the patients with other clinical forms of the disease. A cognitive dysfunction may influence the ability of patients to respond to questionnaires, but the study by Gold et al. suggested that cognitive impairment in MS does not affect the reliability and validity of self-report measures (Gold et al., 2003).

VI. Conclusions

This is the first study that has evaluated the change in the progression index in response to long-term IFNβ-1b therapy. Our results clearly indicate that this long-term continuous immunomodulatory therapy decreases the activity of the disease, influences the progression of MS, and thereby improves the quality of life of MS patients.

The Hungarian version of the MSQOL-54 instrument is well accepted by patients and easy to administer. Its internal consistency reliability measured by Cronbach alpha coefficient is well above the minimum requirement in case of all scales for group-based comparisons and the instrument was able to distinguish between known clinical group differences. On the other hand it is important to emphasise that the questionnaire is not suitable for monitoring individual patients, because it does not meet the much stricter psychometric requirements for this purpose (McHorney and Tarlov, 1995). The self-assessed health-related quality of life of patients provides useful additional information to clinicians.

Multiple sclerosis patient care is a complex task that should not be restricted to monitoring of the physical function and EDSS. The mental health and sexual function are consistently among factors that influence the quality of life of MS patients. The recognition and treatment of depression, a cognitive dysfunction and a sexual dysfunction may improve the overall QoL at a given physical status. Self-reporting quality of life measures, such as the

MSQOL-54, may be useful tools in clinical practice to address symptoms that are not readily captured by the EDSS. This study has yielded quality of life data on more than 400 patients, i.e. a considerable proportion of the MS patient population of Hungary. It is among our aims to examine the instrument in longitudinal studies as well. Other factors influencing quality of life of patients, for example the role of a supporting living environment may also be assessed.

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References

Acquadro, C., Lafortune, L. & Mear, I. (2003) Quality of life in multiple sclerosis: translation in French Canadian of the MSQoL-54. *Health Qual Life Outcomes,* 1**,** 70.

Arbizu, T., Alvarez-Cermeno, J. C., Decap, G., Fernandez, O., Uria, D. F., Garcia Merino, A., Izquierdo, G. & Montalban, X. (2000) Interferon beta-1b treatment in patients with relapsing--remitting multiple sclerosis under a standardized protocol in Spain. *Acta Neurol Scand,* 102**,** 209-17.

Ayatollahi, P., Nafissi, S., Eshraghian, M. R., Kaviani, H. & Tarazi, A. (2007) Impact of depression and disability on quality of life in Iranian patients with multiple sclerosis. *Mult Scler,* 13**,** 275-7.

Aymerich, M., Guillamon, I., Perkal, H., Nos, C., Porcel, J., Berra, S., Rajmil, L. & Montalban, X. (2006) [Spanish adaptation of the disease-specific questionnaire MSQOL-54 in multiple sclerosis patients]. *Neurologia,* 21**,** 181-7.

Banati, M., Sandor, J., Mike, A., Illes, E., Bors, L., Feldmann, A., Herold, R. & Illes, Z. (2010) Social cognition and Theory of Mind in patients with relapsing-remitting multiple sclerosis. *Eur J Neurol,* 17**,** 426-33.

Bencsik, K., Rajda, C., Fuvesi, J., Klivenyi, P., Jardanhazy, T., Torok, M. & Vecsei, L. (2001) The prevalence of multiple sclerosis, distribution of clinical forms of the disease and functional status of patients in Csongrad County, Hungary. *Eur Neurol,* 46**,** 206-9.

Benedict, R. H., Wahlig, E., Bakshi, R., Fishman, I., Munschauer, F., Zivadinov, R. & Weinstock-Guttman, B. (2005) Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *J Neurol Sci,* 231**,** 29-34.

Benito-Leon, J., Morales, J. M. & Rivera-Navarro, J. (2002) Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis patients. *Eur J Neurol,* 9**,** 497-502.

Bergner, M., Bobbitt, R. A., Kressel, S., Pollard, W. E., Gilson, B. S. & Morris, J. R. (1976) The sickness impact profile: conceptual formulation and methodology for the development of a health status measure. *Int J Health Serv,* 6**,** 393-415.

Bobholz, J. A. & Rao, S. M. (2003) Cognitive dysfunction in multiple sclerosis: a review of recent developments. *Curr Opin Neurol,* 16**,** 283-8.

Bronnum-Hansen, H., Koch-Henriksen, N. & Stenager, E. (2004) Trends in survival and cause of death in Danish patients with multiple sclerosis. *Brain,* 127**,** 844-50.

Bullinger, M., Alonso, J., Apolone, G., Leplege, A., Sullivan, M., Wood-Dauphinee, S., Gandek, B., Wagner, A., Aaronson, N., Bech, P., Fukuhara, S., Kaasa, S. & Ware, J. E., Jr. (1998) Translating health status questionnaires and evaluating their quality: the IQOLA Project approach. International Quality of Life Assessment. *J Clin Epidemiol,* 51**,** 913-23.

Calabresi, P. A., Tranquill, L. R., Dambrosia, J. M., Stone, L. A., Maloni, H., Bash, C. N., Frank, J. A. & McFarland, H. F. (1997) Increases in soluble VCAM-1 correlate with a decrease in MRI lesions in multiple sclerosis treated with interferon beta-1b. *Ann Neurol,* 41**,** 669-74.

Carra, A., Onaha, P., Sinay, V., Alvarez, F., Luetic, G., Bettinelli, R., San Pedro, E. & Rodriguez, L. (2003) A retrospective, observational study comparing the four available immunomodulatory treatments for relapsing-remitting multiple sclerosis. *Eur J Neurol,* 10**,** 671-6.

Corsini, E., Gelati, M., Dufour, A., Ciusani, E., La Mantia, L., Massa, G., Milanese, C. & Salmaggi, A. (1999) Reduction of transendothelial migration of mononuclear cells in interferon-beta1b-treated multiple sclerosis patients. *Ann Neurol,* 46**,** 435.

Corsini, E., Gelati, M., Dufour, A., Massa, G., Nespolo, A., Ciusani, E., Milanese, C., La Mantia, L. & Salmaggi, A. (1997) Effects of beta-IFN-1b treatment in MS patients on adhesion between PBMNCs, HUVECs and MS-HBECs: an in vivo and in vitro study. *J Neuroimmunol,* 79**,** 76-83.

Dubois, B. D., Keenan, E., Porter, B. E., Kapoor, R., Rudge, P., Thompson, A. J., Miller, D. H. & Giovannoni, G. (2003) Interferon beta in multiple sclerosis: experience in a British specialist multiple sclerosis centre. *J Neurol Neurosurg Psychiatry,* 74**,** 946-9.

Durelli, L., Verdun, E., Barbero, P., Bergui, M., Versino, E., Ghezzi, A., Montanari, E. & Zaffaroni, M. (2002) Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet,* 359**,** 1453-60.

Ebers, G. C. (2001) Natural history of multiple sclerosis. *J Neurol Neurosurg Psychiatry,* 71 Suppl 2**,** ii16-9.

Ebers, G. C., Reder, A. T., Traboulsee, A., Li, D., Langdon, D., Goodin, D. S., Wolf, C., Beckmann, K. & Konieczny, A. (2009) Long-term follow-up of the original interferon-beta1b trial in multiple sclerosis: design and lessons from a 16-year observational study. *Clin Ther,* 31**,** 1724-36.

Ebers, G. C., Traboulsee, A., Li, D., Langdon, D., Reder, A. T., Goodin, D. S., Bogumil, T., Beckmann, K., Wolf, C. & Konieczny, A. (2010) Analysis of clinical outcomes according to original treatment groups 16 years after the pivotal IFNB-1b trial. *J Neurol Neurosurg Psychiatry,* 81**,** 907-12.

Fruehwald, S., Loeffler-Stastka, H., Eher, R., Saletu, B. & Baumhackl, U. (2001) Depression and quality of life in multiple sclerosis. *Acta Neurol Scand,* 104**,** 257-61.

Gandek, B. & Ware, J. E., Jr. (1998) Methods for validating and norming translations of health status questionnaires: the IQOLA Project approach. International Quality of Life Assessment. *J Clin Epidemiol,* 51**,** 953-9.

Ghaem, H., Borhani Haghighi, A., Jafari, P. & Nikseresht, A. R. (2007) Validity and reliability of the Persian version of the multiple sclerosis quality of life questionnaire. *Neurol India,* 55**,** 369-75.

Gold, S. M., Schulz, H., Monch, A., Schulz, K. H. & Heesen, C. (2003) Cognitive impairment in multiple sclerosis does not affect reliability and validity of self-report health measures. *Mult Scler,* 9**,** 404-10.

Hirst, C., Swingler, R., Compston, D. A., Ben-Shlomo, Y. & Robertson, N. P. (2008) Survival and cause of death in multiple sclerosis: a prospective population-based study. *J Neurol Neurosurg Psychiatry,* 79**,** 1016-21.

Hobart, J., Lamping, D., Fitzpatrick, R., Riazi, A. & Thompson, A. (2001) The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain,* 124**,** 962-73.

Hong, J. & Hutton, G. J. (2010) Regulatory effects of interferon-beta on osteopontin and interleukin-17 expression in multiple sclerosis. *J Interferon Cytokine Res,* 30**,** 751-7.

Huber, S., Spycher, M., Lechner-Scott, J., Bellaiche, Y., Steck, A. J. & Kappos, L. (1996) [Multiple sclerosis: therapy with recombinant beta-1b interferon: initial results with 30 multiple sclerosis patients in northwest Switzerland]. *Schweiz Med Wochenschr,* 126**,** 1475-81.

Idiman, E., Uzunel, F., Ozakbas, S., Yozbatiran, N., Oguz, M., Callioglu, B., Gokce, N. & Bahar, Z. (2006) Cross-cultural adaptation and validation of multiple sclerosis quality of life questionnaire (MSQOL-54) in a Turkish multiple sclerosis sample. *J Neurol Sci,* 240**,** 77-80.

Jacobs, L. D., Cookfair, D. L., Rudick, R. A., Herndon, R. M., Richert, J. R., Salazar, A. M., Fischer, J. S., Goodkin, D. E., Granger, C. V., Simon, J. H., Alam, J. J., Bartoszak, D. M., Bourdette, D. N., Braiman, J., Brownscheidle, C. M., Coats, M. E., Cohan, S. L.,

Dougherty, D. S., Kinkel, R. P., Mass, M. K., Munschauer, F. E., 3rd, Priore, R. L., Pullicino, P. M., Scherokman, B. J., Whitham, R. H. & et al. (1996) Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol,* 39**,** 285-94.

Janardhan, V. & Bakshi, R. (2002) Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. *J Neurol Sci,* 205**,** 51-8.

Janssens, A. C., van Doorn, P. A., de Boer, J. B., van der Meche, F. G., Passchier, J. & Hintzen, R. Q. (2003) Impact of recently diagnosed multiple sclerosis on quality of life, anxiety, depression and distress of patients and partners. *Acta Neurol Scand,* 108**,** 389-95.

Jette, A. M., Davies, A. R., Cleary, P. D., Calkins, D. R., Rubenstein, L. V., Fink, A., Kosecoff, J., Young, R. T., Brook, R. H. & Delbanco, T. L. (1986) The Functional Status Questionnaire: reliability and validity when used in primary care. *J Gen Intern Med,* 1**,** 143-9.

Joffe, R. T., Lippert, G. P., Gray, T. A., Sawa, G. & Horvath, Z. (1987) Mood disorder and multiple sclerosis. *Arch Neurol,* 44**,** 376-8.

Johnson, K. P., Brooks, B. R., Cohen, J. A., Ford, C. C., Goldstein, J., Lisak, R. P., Myers, L. W., Panitch, H. S., Rose, J. W. & Schiffer, R. B. (1995) Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. *Neurology,* 45**,** 1268-76.

Johnson, K. P., Brooks, B. R., Ford, C. C., Goodman, A., Guarnaccia, J., Lisak, R. P., Myers, L. W., Panitch, H. S., Pruitt, A., Rose, J. W., Kachuck, N. & Wolinsky, J. S. (2000) Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years. Copolymer 1 Multiple Sclerosis Study Group. *Mult Scler,* 6**,** 255-66.

Jonsson, A., Dock, J. & Ravnborg, M. H. (1996) Quality of life as a measure of rehabilitation outcome in patients with multiple sclerosis. *Acta Neurol Scand,* 93**,** 229-35.

Khan, O. A., Tselis, A. C., Kamholz, J. A., Garbern, J. Y., Lewis, R. A. & Lisak, R. P. (2001) A prospective, open-label treatment trial to compare the effect of IFN beta-1a (Avonex), IFNbeta-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis. *Eur J Neurol,* 8**,** 141-8.

Kurtzke, J. F. (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology,* 33**,** 1444-52.

Laman, H. & Lankhorst, G. J. (1994) Subjective weighting of disability: an approach to quality of life assessment in rehabilitation. *Disabil Rehabil,* 16**,** 198-204.

Landtblom, A. M., Fazio, P., Fredrikson, S. & Granieri, E. (2010) The first case history of multiple sclerosis: Augustus d'Este (1794-1848). *Neurol Sci,* 31**,** 29-33.

Lankhorst, G. J., Jelles, F., Smits, R. C., Polman, C. H., Kuik, D. J., Pfennings, L. E., Cohen, L., van der Ploeg, H. M., Ketelaer, P. & Vleugels, L. (1996) Quality of life in multiple sclerosis: the disability and impact profile (DIP). *J Neurol,* 243**,** 469-74.

Leray, E., Morrissey, S. P., Yaouanq, J., Coustans, M., Le Page, E., Chaperon, J. & Edan, G. (2007) Long-term survival of patients with multiple sclerosis in West France. *Mult Scler,* 13**,** 865-74.

Lobentanz, I. S., Asenbaum, S., Vass, K., Sauter, C., Klosch, G., Kollegger, H., Kristoferitsch, W. & Zeitlhofer, J. (2004) Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. *Acta Neurol Scand,* 110**,** 6-13.

Lublin, F. D. & Reingold, S. C. (1996) Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology,* 46**,** 907-11.

Lublin, F. D., Whitaker, J. N., Eidelman, B. H., Miller, A. E., Arnason, B. G. & Burks, J. S. (1996) Management of patients receiving interferon beta-1b for multiple sclerosis: report of a consensus conference. *Neurology,* 46**,** 12-8.

Mattson, D., Petrie, M., Srivastava, D. K. & McDermott, M. (1995) Multiple sclerosis. Sexual dysfunction and its response to medications. *Arch Neurol,* 52**,** 862-8.

McHorney, C. A. & Tarlov, A. R. (1995) Individual-patient monitoring in clinical practice: are available health status surveys adequate? *Qual Life Res,* 4**,** 293-307.

McHorney, C. A., Ware, J. E., Jr. & Raczek, A. E. (1993) The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care,* 31**,** 247-63.

Mikol, D. D., Barkhof, F., Chang, P., Coyle, P. K., Jeffery, D. R., Schwid, S. R., Stubinski, B. & Uitdehaag, B. M. (2008) Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *Lancet Neurol,* 7**,** 903-14.

Milanese, C., La Mantia, L., Palumbo, R., Martinelli, V., Murialdo, A., Zaffaroni, M., Caputo, D., Capra, R. & Bergamaschi, R. (2003) A post-marketing study on interferon beta 1b and 1a treatment in relapsing-remitting multiple sclerosis: different response in drop-outs and treated patients. *J Neurol Neurosurg Psychiatry,* 74**,** 1689-92.

Miller, A. & Dishon, S. (2006) Health-related quality of life in multiple sclerosis: The impact of disability, gender and employment status. *Qual Life Res,* 15**,** 259-71.

Murphy, N., Confavreux, C., Haas, J., Konig, N., Roullet, E., Sailer, M., Swash, M., Young, C. & Merot, J. L. (1998) Quality of life in multiple sclerosis in France, Germany, and the United Kingdom. Cost of Multiple Sclerosis Study Group. *J Neurol Neurosurg Psychiatry,* 65**,** 460-6.

O'Connor, P., Filippi, M., Arnason, B., Comi, G., Cook, S., Goodin, D., Hartung, H. P., Jeffery, D., Kappos, L., Boateng, F., Filippov, V., Groth, M., Knappertz, V., Kraus, C., Sandbrink, R., Pohl, C., Bogumil, T., O'Connor, P., Filippi, M., Arnason, B., Cook, S., Goodin, D., Harung, H. P., Kappos, L., Jeffery, D. & Comi, G. (2009) 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. *Lancet Neurol,* 8**,** 889-97.

Onesti, E., Bagnato, F., Tomassini, V., Volante, G., Denaro, F., Frontoni, M., Millefiorini, E., Pozzilli, C. & Fieschi, C. (2003) Interferon beta treatment of MS in the daily clinical setting: a 3-year post-marketing study. *Neurol Sci,* 24**,** 340-5.

Pal, E., Kosztolanyi, P. & Perlaky, P. (2002) [Brain atrophy and cognitive disorder in multiple sclerosis]. *Orv Hetil,* 143**,** 2681-5.

Panitch, H., Goodin, D. S., Francis, G., Chang, P., Coyle, P. K., O'Connor, P., Monaghan, E., Li, D. & Weinshenker, B. (2002) Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. *Neurology,* 59**,** 1496-506.

Parkerson, G. R., Jr., Gehlbach, S. H., Wagner, E. H., James, S. A., Clapp, N. E. & Muhlbaier, L. H. (1981) The Duke-UNC Health Profile: an adult health status instrument for primary care. *Med Care,* 19**,** 806-28.

Patti, F., Cacopardo, M., Palermo, F., Ciancio, M. R., Lopes, R., Restivo, D. & Reggio, A. (2003) Health-related quality of life and depression in an Italian sample of multiple sclerosis patients. *J Neurol Sci,* 211**,** 55-62.

Patti, F., Pozzilli, C., Montanari, E., Pappalardo, A., Piazza, L., Levi, A., Onesti, E. & Pesci, I. (2007) Effects of education level and employment status on HRQoL in early relapsing-remitting multiple sclerosis. *Mult Scler,* 13**,** 783-91.

Paty, D. W. & Li, D. K. (1993) Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. *Neurology,* 43**,** 662-7.

Pekmezovic, T., Kisic Tepavcevic, D., Kostic, J. & Drulovic, J. (2007) Validation and cross-cultural adaptation of the disease-specific questionnaire MSQOL-54 in Serbian multiple sclerosis patients sample. *Qual Life Res,* 16**,** 1383-7.

Peter, T., Zoltan, R., Xenia, G., Bea, S., Nora, S. & Laszlo, K. (2008) [Prevalence of major depression in primary care practices in Hungary]. *Neuropsychopharmacol Hung,* 10**,** 265-70.

Pfennings, L. E., Van der Ploeg, H. M., Cohen, L., Bramsen, I., Polman, C. H., Lankhorst, G. J. & Vleugels, L. (1999) A health-related quality of life questionnaire for multiple sclerosis patients. *Acta Neurol Scand,* 100**,** 148-55.

Piras, M. R., Magnano, I., Canu, E. D., Paulus, K. S., Satta, W. M., Soddu, A., Conti, M., Achene, A., Solinas, G. & Aiello, I. (2003) Longitudinal study of cognitive dysfunction in multiple sclerosis: neuropsychological, neuroradiological, and neurophysiological findings. *J Neurol Neurosurg Psychiatry,* 74**,** 878-85.

Polman, C. H., Bertolotto, A., Deisenhammer, F., Giovannoni, G., Hartung, H. P., Hemmer, B., Killestein, J., McFarland, H. F., Oger, J., Pachner, A. R., Petkau, J., Reder, A. T., Reingold, S. C., Schellekens, H. & Sorensen, P. S. (2010) Recommendations for clinical use of data on neutralising antibodies to interferon-beta therapy in multiple sclerosis. *Lancet Neurol,* 9**,** 740-50.

Porrini, A. M., De Luca, G., Gambi, D. & Reder, A. T. (1998) Effects of an anti-IL-10 monoclonal antibody on rIFNbeta-1b-mediated immune modulation. Relevance to multiple sclerosis. *J Neuroimmunol,* 81**,** 109-15.

Poser, C. M., Paty, D. W., Scheinberg, L., McDonald, W. I., Davis, F. A., Ebers, G. C., Johnson, K. P., Sibley, W. A., Silberberg, D. H. & Tourtellotte, W. W. (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol,* 13**,** 227-31.

PRISMS Study Group (1998) Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet,* 352**,** 1498-504.

Reder, A. T., Ebers, G., Cutter, G., Kremenchutzky, M., Goodin, D., Oger, J., Langdon, D., Rametta, M., Beckmann, K., Knappertz, V. (2010) Survival analysis 21 years after the initiations of the pivotal interferon beta-1b trial in patients with RRMS. *Mult Scler,* 16**,** S318.

Report of the Quality Standards Subcommittee of the American Academy of Neurology (1994) Practice advisory on selection of patients with multiple sclerosis for treatment with Betaseron. *Neurology,* 44**,** 1537-40.

Riazi, A., Hobart, J. C., Lamping, D. L., Fitzpatrick, R. & Thompson, A. J. (2002) Multiple Sclerosis Impact Scale (MSIS-29): reliability and validity in hospital based samples. *J Neurol Neurosurg Psychiatry,* 73**,** 701-4.

Rudick, R. A., Fisher, E., Lee, J. C., Simon, J. & Jacobs, L. (1999) Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Multiple Sclerosis Collaborative Research Group. *Neurology,* 53**,** 1698-704.

Sadovnick, A. D., Remick, R. A., Allen, J., Swartz, E., Yee, I. M., Eisen, K., Farquhar, R., Hashimoto, S. A., Hooge, J., Kastrukoff, L. F., Morrison, W., Nelson, J., Oger, J. & Paty, D. W. (1996) Depression and multiple sclerosis. *Neurology,* 46**,** 628-32.

Sfagos, C., Papageorgiou, C. C., Kosma, K. K., Kodopadelis, E., Uzunoglu, N. K., Vassilopoulos, D. & Rabavilas, A. D. (2003) Working memory deficits in multiple sclerosis: a controlled study with auditory P600 correlates. *J Neurol Neurosurg Psychiatry,* 74**,** 1231-5.

Simeoni, M., Auquier, P., Fernandez, O., Flachenecker, P., Stecchi, S., Constantinescu, C., Idiman, E., Boyko, A., Beiske, A., Vollmer, T., Triantafyllou, N., O'Connor, P., Barak, Y., Biermann, L., Cristiano, E., Atweh, S., Patrick, D., Robitail, S., Ammoury, N., Beresniak, A. & Pelletier, J. (2008) Validation of the Multiple Sclerosis International Quality of Life questionnaire. *Mult Scler,* 14**,** 219-30.

Simon, J. H., Jacobs, L. D., Campion, M., Wende, K., Simonian, N., Cookfair, D. L., Rudick, R. A., Herndon, R. M., Richert, J. R., Salazar, A. M., Alam, J. J., Fischer, J. S., Goodkin, D. E., Granger, C. V., Lajaunie, M., Martens-Davidson, A. L., Meyer, M., Sheeder, J., Choi, K., Scherzinger, A. L., Bartoszak, D. M., Bourdette, D. N., Braiman, J., Brownscheidle, C. M., Whitham, R. H. & et al. (1998) Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. *Ann Neurol,* 43**,** 79-87.

Smestad, C., Sandvik, L. & Celius, E. G. (2009) Excess mortality and cause of death in a cohort of Norwegian multiple sclerosis patients. *Mult Scler,* 15**,** 1263-70.

Solari, A., Ferrari, G. & Radice, D. (2006) A longitudinal survey of self-assessed health trends in a community cohort of people with multiple sclerosis and their significant others. *J Neurol Sci,* 243**,** 13-20.

Solari, A., Filippini, G., Mendozzi, L., Ghezzi, A., Cifani, S., Barbieri, E., Baldini, S., Salmaggi, A., Mantia, L. L., Farinotti, M., Caputo, D. & Mosconi, P. (1999) Validation of Italian multiple sclerosis quality of life 54 questionnaire. *J Neurol Neurosurg Psychiatry,* 67**,** 158-62.

Somerset, M., Peters, T. J., Sharp, D. J. & Campbell, R. (2003) Factors that contribute to quality of life outcomes prioritised by people with multiple sclerosis. *Qual Life Res,* 12**,** 21-9.

Sorensen, P. S., Deisenhammer, F., Duda, P., Hohlfeld, R., Myhr, K. M., Palace, J., Polman, C., Pozzilli, C. & Ross, C. (2005) Guidelines on use of anti-IFN-beta antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-beta antibodies in multiple sclerosis. *Eur J Neurol,* 12**,** 817-27.

Sumelahti, M. L., Hakama, M., Elovaara, I. & Pukkala, E. (2010) Causes of death among patients with multiple sclerosis. *Mult Scler,* 16**,** 1437-42.

The EuroQol Group (1990) EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy,* 16**,** 199-208.

The IFNB Multiple Sclerosis Study Group (1993) Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology,* 43**,** 655-61.

Uhm, J. H., Dooley, N. P., Stuve, O., Francis, G. S., Duquette, P., Antel, J. P. & Yong, V. W. (1999) Migratory behavior of lymphocytes isolated from multiple sclerosis patients: effects of interferon beta-1b therapy. *Ann Neurol,* 46**,** 319-24.

Vernay, D., Gerbaud, L., Biolay, S., Coste, J., Debourse, J., Aufauvre, D., Beneton, C., Colamarino, R., Glanddier, P. Y., Dordain, G. & Clavelou, P. (2000) [Quality of life and multiple sclerosis: validation of the french version of the self-questionnaire (SEP-59)]. *Rev Neurol (Paris),* 156**,** 247-63.

Vickrey, B. G., Hays, R. D., Harooni, R., Myers, L. W. & Ellison, G. W. (1995) A health-related quality of life measure for multiple sclerosis. *Qual Life Res,* 4**,** 187-206.

Wallin, M. T., Page, W. F. & Kurtzke, J. F. (2000) Epidemiology of multiple sclerosis in US veterans. VIII. Long-term survival after onset of multiple sclerosis. *Brain,* 123 (Pt 8)**,** 1677-87.

Ware JE, J., Kosinski M, Gandek, B. (1993) *SF-36 Health Survey: Manual and Interpretation Guide*, Lincoln, RI: QualityMetric Incorporated.

Ware, J. E., Jr. & Gandek, B. (1998) Methods for testing data quality, scaling assumptions, and reliability: the IQOLA Project approach. International Quality of Life Assessment. *J Clin Epidemiol,* 51**,** 945-52.

Ware, J. E., Jr. & Sherbourne, C. D. (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care,* 30**,** 473-83.

Ware JE, K. M., Dewey JE. (2000) *How to score Version 2 of the SF-36 Health Survey*, Lincoln, RI: QualityMetric Incorporated.

Yamamoto, T., Ogata, K., Katagishi, M., Shimizu, H., Ogawa, M., Yamamura, T. & Kawai, M. (2004) [Validation of the Japanese-translated version Multiple Sclerosis Quality of Life-54 instrument]. *Rinsho Shinkeigaku,* 44**,** 417-21.

Zivadinov, R., Zorzon, M., Locatelli, L., Stival, B., Monti, F., Nasuelli, D., Tommasi, M. A., Bratina, A. & Cazzato, G. (2003) Sexual dysfunction in multiple sclerosis: a MRI, neurophysiological and urodynamic study. *J Neurol Sci,* 210**,** 73-6.