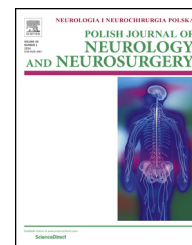


Available online at www.sciencedirect.com

ScienceDirect

journal homepage: <http://www.elsevier.com/locate/pjnns>

Review article

Does interferon beta therapy affect survival of multiple sclerosis patients?



Alina Kułakowska*, Wiesław Drozdowski

Department of Neurology, Medical University of Białystok, Białystok, Poland

ARTICLE INFO

Article history:

Received 6 October 2014

Accepted 9 October 2014

Available online 23 October 2014

Keywords:

Multiple sclerosis

Mortality

Immodulatory treatment

Interferon beta

ABSTRACT

Multiple sclerosis (SM) is a chronic inflammatory and degenerative disease of the central nervous system. Its etiology has not been fully elucidated. For approximately 20 years, drugs have been used, successfully modifying the natural course of relapsing-remitting SM. One of them is interferon beta. Research outcomes of 16- and 21-year-retrospective follow-up of patients who participated in the pivotal interferon beta-1b trial were reported in 2010 and 2012, respectively. After 21 years, mortality rate among patients treated in the first 5 years with interferon beta-1b at a dose of 250 µg was significantly lower, irrespective of the cause, as compared to the placebo-controlled group. Interferon beta-1b administered during the first 5 years of the study decreased the risk of death by 46.8% as compared to the placebo patients. Moreover, the studies also confirmed safety of long-term interferon beta-1b therapy. However, not much is known about the effect of interferon beta-1a on patients' survival – the available data are presented in the article.

© 2014 Polish Neurological Society. Published by Elsevier Urban & Partner Sp. z o.o. All rights reserved.

1. Life expectancy of patients with multiple sclerosis – is it a marginalized problem?

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system (CNS) affecting mainly the young [1,2]. Since its etiology still remains not completely clear, there is no effective causative treatment [3]. In most patients, the disease leads to psychophysical disability that reduces the quality of life [4,5]. Permanent disability arouses the greatest fear among MS patients and their families. On the other hand, a potential reduction in life expectancy is relatively seldom discussed both by patients and doctors. It is commonly believed that MS reduces life quality

but virtually has no impact on life expectancy. Statements of that kind can be found on the websites of MS support groups in various countries, like the one of the Polish Society of Multiple Sclerosis (PTSR in Polish): *However, MS does not affect life expectancy, being nearly the same as the average length of human life* [6]. Multiple sclerosis is highly heterogenic, and cases may differ extremely in clinical symptoms, course and severity. Therefore, long-term registry studies, possibly covering the whole population of patients in the respective country or region can serve as the source of information on the natural course of MS [7]. Danish Multiple Sclerosis Registry established in 1956 is one of the oldest of that type worldwide [8,9]. Since the Registry includes all Danish citizens diagnosed with MS, it is highly reliable. The analysis of mortality data

* Corresponding author at: Department of Neurology, University Hospital, Ul. Skłodowskiej-Curie 24a, 15-276 Białystok, Poland. Tel.: +48 85 7468326; fax: +48 85 7468608.

E-mail address: alaku@umb.edu.pl (A. Kułakowska).

<http://dx.doi.org/10.1016/j.pjnns.2014.10.003>

0028-3843/© 2014 Polish Neurological Society. Published by Elsevier Urban & Partner Sp. z o.o. All rights reserved.

suggests that life expectancy among MS patients in Denmark is 10–12 years shorter compared to the general population, and in over 50% of the deceased, MS is the reported cause [10]. The standardized mortality ratio (SMR) is a ratio of the number of observed deaths in the disease burden group to the number of deaths in burden-free group. The SMR above 1.0 indicates an unfavorable effect of the disease on patients' survival. According to the Danish Registry, SMR in the MS group is 3.14 for women and 2.66 for men [11], as compared to the SMR in an early breast cancer period 2.0, cirrhosis 2.52 and diabetes 4.47 [12,13].

2. Life expectancy of MS patients in Poland

In Poland, MS cases are not registered on a regular basis, and epidemiological data on the disease are confined to the results obtained in a few population studies conducted in chosen regions of the country or in pilot trials covering approximately 15% of the entire population of Polish patients [14–17]. However, in 2011 some extremely interesting findings were reported on life expectancy in MS patients in Poland; unfortunately, the report was published in a minor journal. Cendrowski [18] carried out a retrospective study to analyze a long-term tendency of changes in life expectancy and in C-PSI (*Case-to-Population Survival Index*) among MS patients who had died in Poland within nearly a 40-year-period (1969–2007). The C-PSI was calculated as a quotient of the average age at death and life expectancy of the Polish population in the same calendar year. The researcher, using statistical data of WHO and Central Statistical Office (GUS in Polish) analyzed 18,703 deaths, in which MS was a primary or secondary cause. In the study period, the average lifespan extended from 49.4 to 56.5 years in MS male patients and from 49.2 to 56.4 years in the female ones. However, C-PSI did not change significantly: the Index was found to be 0.72 for women and 0.79 for men in 1969 versus 0.70 and 0.78 in 2007, respectively. This indicates a simultaneous increase in life expectancy of MS patients and in the general population. Eventually, survival rate among male and female MS sufferers at the end of the study period (2007) was respectively by 15 and 23 years shorter (Fig. 1) as compared to the general population [18].

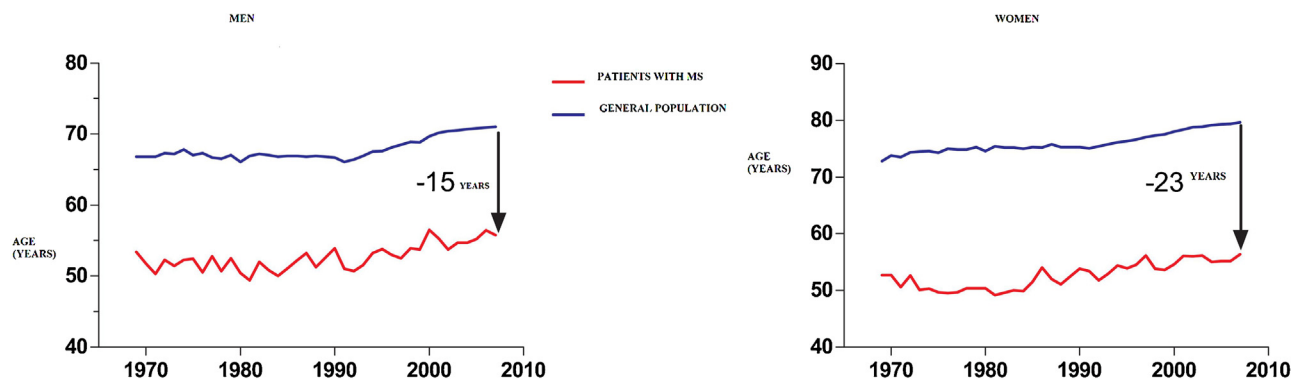


Fig. 1 – Curves illustrating the median survival of MS patients in comparison to the general population in Poland, in the years 1969–2007.

Figure from the article: Cendrowski W., *Terapie specjalistyczne*. Bayer HealthCare 2011; 1(1): 18–24.

3. Long-term assessment of immunomodulatory treatment

Drugs that substantially modify the natural course of relapsing-remitting MS (decreasing the relapse rate and inhibiting disability progression) have been used for only 20 years now. Registration of the first preparation, interferon beta, in the 1990s was a breakthrough in the treatment of MS [19]. Interferon beta preparations [20,21] were registered after 24-month multi-center, randomized, double blind, clinical trials which proved short-term efficacy and safety of the drugs in comparison with placebo, yet did not elucidate their long-term effects (?). Nowadays, the available registries of patients also fail to settle the issue [7]; they show, however, that disability progresses in a predictable manner when EDSS is over 4, independently of the initial course of the disease [22,23]. This proves that the therapy should be instituted early enough to slow down the progression. It seems that the impact of the immunomodulatory therapy on the natural course of MS can only be assessed based on well-planned clinical trials interpreted in the context of patient registry data. Long-term research of patients undergoing immunomodulatory therapy provides valuable information on its efficacy and safety.

4. Long-term follow-up of patients treated with interferon beta-1b

4.1. A 16-year retrospective study

In June 2010, results were reported of a 16-year retrospective follow-up of patients involved in the clinical research that initiated interferon 1b marketing in 1993 [24]. Patients with relapsing-remitting MS participating in the pivotal study ($n = 372$) were randomly assigned to 3 study groups, each receiving either placebo or interferon beta 1b 50 μg or interferon beta 1b 250 μg subcutaneously every other day. The aim of the retrospective follow-up was to find out any differences between the three groups 16 years after the commencement of the pivotal study. Data were collected on the level of disability as determined by the *Expanded Disability*

Status Scale (EDSS) [25] and the Multiple Sclerosis Functional Composite Measure (MSFC) [26], relapse rates and conversion to secondary-progressive MS.

The authors [24] managed to identify 328 out of 372 (88.2%) patients involved in the pivotal study, among whom 35 turned out to be deceased (35/328; 10.7%). The analysis of the three baseline groups of patients (placebo, interferon beta 1b 250 µg or interferon beta 1b 50 µg) showed evident differences in mortality rate. Of the 35 deceased patients, twenty had been in the placebo group (20/109; 18.3%), nine had received interferon beta 1b at a dose of 50 µg (9/108; 8.3%), and six interferon beta 1b 250 µg (6/111; 5.4%). Interestingly, the cause of death was known only in 9 out of the 35 cases.

4.2. A 21-year retrospective follow-up study

As patients treated with interferon beta 1b from the very beginning seemed more likely to survive than those receiving placebo, an attempt was made to assess all the patients participating in the pivotal trial after 21.4 years on average following randomization [27]. The researchers managed to identify 366 patients (98.4%), of whom 81 were deceased (37 received placebo at baseline; 22 – interferon 50 µg and 22 – interferon 250 µg). After 21 years, mortality rate was significantly lower in patients treated with a higher dose of interferon beta 1b at baseline, irrespective of the cause, as compared to the placebo group ($p = 0.0173$). The drug decreased the risk of death by 46.8% in comparison with the patients receiving placebo within the first 5 years of the study (Fig. 2).

The lower dose of interferon beta 1b (50 µg) had a similar beneficial effect on the survival rate [27]. Apparently, the effect of the drug on patients' survival is not dose-dependent. Theoretically, this effect may be associated with antioxidant properties of the drug; however, the issue requires further research. The mortality rate in the placebo

group at baseline was consistent with the data concerning the natural course of MS obtained from patient registries. Moreover, the fact that the immunomodulatory therapy applied after the baseline study termination did not differ significantly between the three baseline groups (placebo, interferon beta 1b 250 µg, interferon beta 1b 50 µg) also seems to emphasize a beneficial effect of interferon beta 1b on patients' survival.

The cause of death was established in 61 (75.3%) cases – no significant differences were noted with respect to the cause of death in the respective baseline groups. In 50 (82%) out of 61 cases the cause of death was associated with MS (EDSS > 7, brain stem dysfunction, aspiration pneumonia, sepsis, respiratory failure, pulmonary embolism, trauma caused by a fall, side-effects of treatment, suicide) [27].

Not only treatment-related benefits, but also certain baseline parameters, such as lower EDSS score, smaller MRI ventricle size and smaller T2 lesion volume were associated with longer survival [27].

The 21-year follow-up positively verified the results obtained after 16 years. The NNT index (*Number needed to treat*) calculated on the basis of the obtained results was 7.78, which indicates that statistically 8 patients have to be treated with interferon beta-1b for 21 years, to prevent one fatal outcome. For instance, NNT for statins administered for 5 years to patients with coronary disease to prevent death is 83 and for antiplatelet drugs in acute stroke to prevent death – 100 [28].

The 21-year study revealed the importance of the appropriate length of follow-up and showed that data should be obtained from the highest possible percentage of originally randomized patients [27]. In the additional 5-year-observation period, the number of deaths doubled (35 after 16 years and 81 after 21 years). It also turned out that the mortality rate in the initially unidentified patients was higher than that noted among the identified cases (18.4% vs. 10.7%).

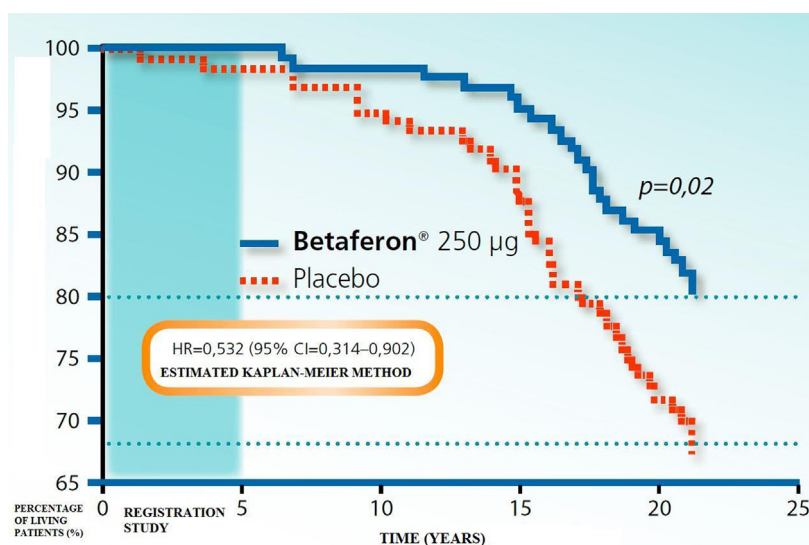


Fig. 2 – Curves illustrating survival of patients within a 21-year-period, at the beginning of the pivotal study, treated with interferon beta 1b and placebo.

Figure from the article: Michalak S., *Terapie specjalistyczne*. Bayer HealthCare 2011; 2(2): 8–12. For writing this review article the authors did not receive any financial support.

4.3. A long-term follow-up of patients treated with interferon beta-1a

4.3.1. A retrospective 15-year follow-up of patients treated with intramuscular interferon beta-1a therapy

Patients were assessed 15 years after randomization into the registration trial of interferon beta-1a administered intramuscularly in relapsing-remitting SM [29]. The study used the EDSS; life quality and independence-related questionnaires were applied. Data were obtained for 79% of eligible patients (136/172). Patients currently receiving intramuscular interferon beta-1a presented significantly lower EDSS scores, less progression to the EDSS threshold (EDSS = 6), better general health condition and greater independence.

Fourteen patients out of 136 died, including 8 who had been given placebo at baseline and 6 treated with interferon beta-1a. The mean time to death since enrollment to the study showed a tendency toward statistical significance ($p = 0.0584$). In the case of 8 patients who had been allocated to the placebo group at baseline, the mean time to death was 7.8 years, whereas in 6 patients receiving interferon beta – 11.5 years.

4.3.2. Retrospective 8-year and 15-year follow-up studies of patients treated with subcutaneous interferon beta-1a therapy

Patients participating in the registration trial of interferon beta-1a administered subcutaneously 3 times a week were assessed 8 years after randomization [30]. Only 68.2% of the patients (382/560) returned for the long-term follow-up assessment. In the interferon beta-1a 44 μg group, patients presented with lower EDSS score, lower annual relapse rate and smaller T2 lesion volume, as compared to the baseline placebo group. Of 382 patients who did not return for the assessment 8 years after randomization, eight were deceased, including two assigned to the placebo group at baseline, five taking interferon beta-1a 22 μg and one – interferon beta-1a 44 μg . Three out of these 8 deaths took place during the registration trial (not related to the assessed drug) and the other five after its termination (unknown cause).

In 2012, results of the assessment of mortality and its predictors 15 years after the initial randomization into the baseline subcutaneous interferon beta-1a group were published as a conference report [31]. In the assessed group, there were 26 deaths; however, the mortality rate did not differ significantly between the 3 baseline groups (placebo, interferon 22 μg and 44 μg). Age, EDSS and T2 lesion volume at the time of randomization were found to significantly affect mortality.

The authors of the publication [31] managed to identify only 291 patients from the registration study (291/560; 52%). Thus, it cannot be excluded that among the remaining 269 patients (48%), the percentage of deaths could be even higher, like it was in the 16-year follow-up of interferon beta-1b therapy. Potential data obtained from the non-assessed patients might alter the proportional distribution of deaths in the three baseline study groups.

4.4. Long-term treatment with interferon beta and life expectancy of patients

Only the long-term (21-year) follow-up of patients randomized at baseline to the registration study provides mortality-related

data, indicating a beneficial effect of the drug [27]. Other long-term observations of patients treated with interferon beta preparations, yet substantially shorter and involving a lower percentage of patients at baseline, almost neglect that issue. However, in a study on intramuscular interferon beta-1a therapy, trends in mortality seem to confirm the benefits of early treatment with the drug [29]. On the other hand, a 15-year follow-up of subcutaneous interferon beta-1a therapy that involved only 52% of baseline trial patients does not support this view [31].

The problem of mortality has not been raised in open trials such as QUASIMS (*Quality Assessment in Multiple Sclerosis Therapy*) [32], assessing the efficacy and safety of various interferon beta preparations. Their survey was discussed in detail by Limmoroth et al. [33]. Most of the studies have not revealed any significant differences in the efficacy of the respective interferon beta preparations, which seems to confirm their similar impact on mortality rate. This, however, requires further research.

4.5. Life expectancy and life quality

In the discussion on patients' survival, the problem of life quality cannot be avoided. As shown in numerous reports, the quality of life is significantly reduced in MS patients, undergoing gradual deterioration with progressing disability [4,34]. However, Putzki et al. have revealed that the quality of life is already significantly decreased in the early phases of the disease and that it can be improved by immunomodulatory therapy at that stage [5].

So far, reports from the 21-year follow-up have not elucidated whether early administration of interferon beta-1b not only increases the chances of survival but also prevents disability. However, the 16-year-observation has shown some beneficial impact of long-term t interferon beta-1b therapy on disability [24]. The analysis of 3 subgroups of patients that differed in the time of exposure to interferon beta-1 b 250 μg (<10%; 10–79% and \geq 80% of the observation period) failed to find statistically significant differences in the EDSS score, although the time from diagnosis to EDSS \geq 6.0 was longer in the group of patients with the longest exposure to the drug (13.6 years for \geq 80%, 10.5 years for 10–79% and 8.3 years for <10% of the follow-up period). The incidence rate of the secondary-progressive type (34.3% in the group of patients treated <10% and 28.6% with \geq 80% of the of the follow-up period) was found to be lower (statistically insignificant) and the time from diagnosis to that moment was prolonged (11.4 years for <10% and 13.8 years for \geq 80% of the follow-up). The respective groups did not differ in the annual relapse rate, which decreased in all study groups as compared to the baseline level (1.6–1.8 to 0.3–0.6 after 15–16 years since the commencement of the study).

Maintenance of psychophysical efficiency is not the only determinant of life quality. The term “life quality” itself is ambiguous and multifactorial, depending on cultural and social differences, and general social standards [35]. Studies on the quality of life have shown that MS patients exhibit high level of psychological adaptation to the disease. In a Swedish study [4] no correlation was found between the enhancement of psychosocial problems and the disease progression. Also

research conducted in Poland using a EQ-5D questionnaire revealed that with time patients mostly reported mobility difficulties, but not anxiety/depression problems.

4.6. Safety of long-term interferon beta therapy

Safety of long-term immunomodulatory therapy in multiple sclerosis is an equally important issue. All so far conducted long-term studies assessing the effects of interferon beta preparations confirm their safe use [29,30,36]. The 16-year follow-up [24] has proved the safety of long-term interferon beta-1b therapy, with the most frequent side-effects being flu-like symptoms, fever, headaches, reactions at the site of drug administration (necrotic lesions were not observed), general malaise, muscle pains, slight lymphopenia and elevated level of hepatic enzymes. The frequency of side effects associated with interferon beta-1b therapy decreased with time, being lower within the last 2 years of the 16-year-follow-up as compared to the baseline (pivotal trial). Moreover, no other new side-effects appeared after 16 years of drug administration [36]. Similar findings were reported from an eight-year follow-up of subcutaneous interferon beta-1a therapy [30], during which the most common were mild or moderate reactions at the site of drug injection (in 44%) and flu-like symptoms (in 11.7% of patients). In laboratory studies, the most frequent but usually mild abnormalities included the elevated level of transaminases and lymphopenia [30].

4.7. Disadvantages of retrospective trials

Although retrospective observations of patients provide valuable information on the efficacy and safety of the treatment applied, they have a number of limitations that hinder interpretation of results. For instance, incomplete identification of patients or non-returning patients can reduce the power of the study and deform the outcome. Another problem is lack of randomization and control, as well as treatment adherence which is difficult to reliably assess during a long-term retrospective follow-up study. The cited publications do not analyze this issue [24,27,29,30]. It has been estimated that even one fourth of all SM patients do not comply with dosing recommendations [37]. Significantly, many patients may also use other immunomodulatory drugs than the one assessed, which is likely to affect both the clinical picture of the disease and the side-effects observed.

5. Conclusion

Until now, all follow-up trials involving MS patients treated with interferon beta have demonstrated long-term efficacy of the therapy, suggesting a positive impact of interferon beta-1b on patients' survival. Long-term treatment with interferon beta has proved to be safe and proper monitoring helps avoid serious undesirable effects. According to the available data, the interferon beta therapy should be continued as long as it is efficient and well tolerated. In the last decade, new immunomodulatory drugs, such as natalizumab, fingolimod and teriflunomid have been registered as a favorable alternative

when interferon beta is inefficient. However, data concerning the effects of long-term treatment with these preparations are currently missing.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES

- [1] Weinschenker BG, Bass B, Rice G, Noseworthy J, Carriere W, Baskerville J, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain* 1989;112:133-46.
- [2] Compston A, Coles A. Multiple sclerosis. *Lancet* 2002;359:1221-31.
- [3] Putzki N, Hartung HP. Disease modifying treatment in MS. W: Putzki N, Hartung HP. [red.] Treatment of multiple sclerosis. Wyd. 1. Bremen: UNI-MED; 2009. p. 38-63.
- [4] Gotteberg K, Einarsson U, Ytterberg C, de Pedro Cuesta J, Fredrikson S, von Koch L, et al. Health-related quality of life in a population-based sample of people with multiple sclerosis in Stockholm county. *Mult Scler* 2006;12:605-12.
- [5] Putzki N, Fischer J, Gottwald K, Ries S, Siever A, Hoffmann F, et al. Quality of life in 1000 patients with early relapsing-remitting multiple sclerosis. *Eur J Neurol* 2009;16:713-20.
- [6] www.msif.org.pl.
- [7] Hurwitz BJ. Registry studies of long-term multiple sclerosis outcomes. *Neurology* 2011;76(Suppl. 1):S3-6.
- [8] Koch-Henriksen N. The Danish Multiple Sclerosis Registry: a 50-year follow-up. *Mult Scler* 1999;5:293-6.
- [9] Koch-Henriksen N, Rasmussen S, Stenager E, Madsen M. The Danish Multiple Sclerosis Registry: history, data collection, and validity. *Dan Med Bull* 2001;48:91-4.
- [10] Bronnum-Hansen H, Koch-Henriksen N, Hyllested K. Survival of patients with multiple sclerosis in Denmark: a nationwide long-term epidemiologic survey. *Neurology* 1994;44:1901-7.
- [11] Bronnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. *Brain* 2004;12:844-50.
- [12] De Marco R, Locatelli F, Zoppini G, Verlatto G, Bonora E, Muggeo M. Cause-specific mortality in type 2 diabetes. The Verona Diabetes Study. *Diabetes Care* 1999;22:756-61.
- [13] Hoening MJ, Aleman BM, van Rosmalen AJ, Kuenen MA, Klijn JG, van Leeuwen FE. Cause-specific mortality in long-term survivors of breast cancer: a 25-year follow-up study. *Int J Radiat Oncol Biol Phys* 2006;64:1081-91.

- [14] Łobińska A, Stelmasiak Z. Wybrane epidemiologiczne aspekty stwardnienia rozsianego w populacji miasta Lublina. *Neurol Neurochir Pol* 2004;38(5):361–6.
- [15] Potemkowski A. Analiza epidemiologiczna stwardnienia rozsianego w województwie szczecińskim: ocena zachorowalności i chorobowości w latach 1993–1995. *Neurol Neurochir Pol* 1999;33(3):34–44.
- [16] Wender M, Kowal P, Pruchnik-Grabowska D, Marcinkowski J, Hertmanowska H, Namysł I, et al. Stwardnienie rozsiane – rozpowszechnienie i zapadalność wśród ludności miejscowej w zachodniej Polsce. *Neurol Neurochir Pol* 1987;21(1):33–9.
- [17] Kułakowska A, Bartosik-Psujek H, Hożejowski R, Mitosek-Szewczyk K, Drozdowski W, Stelmasiak Z. Selected aspects of the epidemiology of multiple sclerosis in Poland – a multicentre pilot study. *Neurol Neurochir Pol* 2010;44(5):443–52.
- [18] Cendrowski W. Analiza wskaźnika przeżywalności w polskiej populacji chorych na stwardnienie rozsiane – w perspektywie wieloletniej. *Terapie specjalistyczne*. Bayer Healthc 2011;1(1):18–24.
- [19] The INFB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993;43:655–61.
- [20] Jacobs L, Cookfair D, Rudick R, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta 1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996;39:285–94.
- [21] PRISM Group. Randomised double-blind placebo-controlled study of interferon beta 1a in relapsing/remitting multiple sclerosis. *Lancet* 1998;352:1498–504.
- [22] Kremenchutzky M, Rice GPA, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: a geographically based study: 9: Observations on the progressive phase of the disease. *Brain* 2006;129:584–94.
- [23] Confavreux C, Vucosic S. Natural history of multiple sclerosis: a unifying concept. *Brain* 2006;129:606–16.
- [24] Ebers GC, Traboulsee A, Li D, Langdon D, Reder AT, Goodin DS, et al. Analysis of clinical outcomes according to original treatment groups 16 years after the pivotal INFB-1b trial. *J Neurol Neurosurg Psychiatry* 2010;81:907–12.
- [25] Kurtzke JF. Rating neurological impairment in multiple sclerosis; an expanded disability status scale (EDSS). *Neurology* 1983;33:1444–52.
- [26] Rudick RA, Cutter G, Baier M, Fisher E, Dougherty D, Weinstock-Guttman B, et al. Use of the multiple sclerosis functional composite to predict disability in relapsing MS. *Neurology* 2001;56:1324–30.
- [27] Goodin DS, Reder AT, Ebers GC, Cutter G, Kremenchutzky M, Oger J, et al. Survival in MS. *Neurology* 2012;78:1315–22.
- [28] <http://www.thennt.com/>.
- [29] Bermel RA, Weinstock-Guttman B, Bourdette D, Foulds P, You X, Rudick R. Intramuscular interferon beta-1a therapy in patients with relapsing-remitting multiple sclerosis: a 15 year follow-up study. *Mult Scler* 2010;16:588–96.
- [30] Kappos L, Traboulsee A, Constantinescu C, Eralinna JP, Forrester F, Jongen P, et al. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. *Neurology* 2006;67:944–53.
- [31] Cornelisse P, Lehr L, Baldinetti F. Baseline predictors of mortality in patients with relapsing-remitting multiple sclerosis: exploratory analyses from the PRISMS-15 study. 28th ECTRIMS, 10–13 October, Lyon, France, Poster. 2012;521.
- [32] Limmoroth V, Malessa R, Zettel UK, Koehler J, Japp G, Haller P, et al. Quality assessment in multiple sclerosis therapy (QUASIMS). *J Neurol* 2007;254:67–77.
- [33] Limmoroth V, Putzki N, Kachuck NU. The interferon beta therapies for treatment of relapsing-remitting multiple sclerosis: are they equally efficacious? A comparative review of open-label studies evaluating the efficacy, safety, or dosing of different interferon beta formulations alone or in combination. *Ther Adv Neurol Disord* 2011;4(5):281–96.
- [34] Forbes RB, Lees A, Waugh N, Swingler RJ. Population based cost utility study of interferon beta-1b in secondary progressive multiple sclerosis. *Br Med J* 1999;319:1529–33.
- [35] Hunt SM. The problem of quality of life. *Qual Life Res* 1997;6(3):205–12.
- [36] Reder AT, Ebers GA, Traboulsee A, Li D, Langdon DS, Goodin T, et al. Cross-sectional study assessing long-term safety of interferon beta 1b for relapsing-remitting MS. *Neurology* 2010;74:1877–85.
- [37] Devonshire V, Lapierre Y, Macdonell R, Romo-Tello C, Patti F, Fontarura R, et al. The global adherence project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. *Eur J Neurol* 2011;18(1):69–77.