Disease activity and disability evolution under glatiramer acetate: A clinical approach

Vitalie Văcăraș[2,3]*, Zoltán Zsigmond Major[1,4]*, Ritesh Seewooram[3], Kinga Andrea Major[3], Dafin Fior Muresanu[2,3]** and Anca Dana Buzoianu[1]**

[1] *Dept. of Pharmacology, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania*
[2] *Dept. of Neurosciences, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania*
[3] *Cluj County Emergency Hospital, Cluj-Napoca, Romania*
[4] *Municipal Clinical Hospital, Cluj-Napoca, Romania*
* *Equal contributions*
** *Equal contributions*

Introduction: By analyzing literature data regarding glatiramer acetate in the treatment of relapsing-remitting multiple sclerosis one might find controversial data but the majority of authors state that the clinical evolution under the treatment showes a positive course. **Materials and methods:** Our goal was to analyze groups of patients, both non-treated and treated with the drug, for relapse rate, Kurtzke's Expanded Disability Status Scale (EDSS) score, Multiple Sclerosis Functional Composite (MSFC) score – upper limb disability, lower limb disability and cognition, and for cognitive dysfunction, using the Montreal Cognitive Assessment (MoCA) test, in order to objectively quantify the clinical impact of the drug. **Results/ Conclusions:** Our results are in accordance with the literature for most of the investigated measures – relapse rate, EDSS, MSFC –, and furthermore suggest the possibility to use more extensively the MoCA test for evaluation of MS patients from the point of view of cognitive functions, after a much wider comparative assessment.
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Keywords: relapsing-remitting multiple sclerosis, EDSS, MSFC, MoCA, glatiramer acetate

Multiple sclerosis is a demyelinating disease affecting young adults which may lead to severe disability and finally to death. Its severe evolutionary character has no satisfactory therapeutical control by any of the available treatments including steroids for the treatment of relapses as well as disease modifying medications. Although these remedies reduce severity and frequency of relapses in relapsing-remmitting multiple sclerosis (RRMS), the lack of efficacy is almost total in case of progressive clinical forms.

One of the frequently used disease modifying drugs is glatiramer acetate, an interesting polymer composed of four amino acids which holds apparently varied and controversial mechanisms of action – the modulation of the immune response, molecular mimicry for some proteins of the CNS, "boost" for neuroprotection etc. (Aharoni, 2012) – and which presents a divergent impact on the evolution of RRMS. In case of paraclinical investigations results can't be interpreted as favorable in most circumstances, although in diverse studies there was some positive evidence for batteries of neurophysiological (Maier et al., 2006) and imagery assessments (Cadavid et al., 2009). Sometimes technical limits do not allow obtaining a quantifiable evaluation of the answer (Zivadinov et al., 2012). In spite of this, we note one aspect: the clinical evolution of the patients is better under treatment, as we mentioned previously, disjunctive towards the instrumental evaluation (Khan et al., 2001; Johnson, 2012).

For the objective quantification of clinical evolution the necessity for different assessment tools has been formulated (Noseworthy, 1994). The annual rate of relapses is a useful measure for disease activity, but doesn't provide information regarding disability. Kurtzke's Expanded Disability Status Scale (EDSS)

was proposed as a way of evaluation for disability and it is still the most used scale in clinical studies, although there have been issues regarding its standardization (Hobart et al., 2000), and the EDSS does not excel through fine and differentiated evaluation of motor disabilities and practically the possibility of cognitive evaluation is missing (Hoogervorst et al., 2003). For achieving this desideratum a new scale has been developed and proposed called Multiple Sclerosis Functional Composite (MSFC) (Fischer et al., 1999). This scale covers three dimensions – timed 25 foot walk test, through which it evaluates the disability of the lower limbs; 9-hole peg test used for testing the disability of upper limbs, and finally PASAT (paced auditory serial addition test), which provides assessment for information processing, auditory and calculation skills (Rudick et al., 2002). MSFC seems to be the most sensitive evaluation scale for disability in MS by this date, and, as a consequence, is the most frequently used instrument in clinical trials (Ozakbas et al., 2004). For cognitive evaluation other tests might also be used, like the Montreal Cognitive Assessment (MoCA) test. MoCA is considered to be a quick test in order to investigate different cognitive fields including attention, memory, speech, executive functions etc. (Dagenais et al., 2013).

Functional deficits are evolving at quite an alerting rate if disease is examined during its natural course, being good candidates for monitoring disease progression, and also valuable parameters for evaluating clinical efficacy of disease modifying drugs including glatiramer acetate, as stated for many years already (Johnson et al.; 1995, 2000). On the other hand, cognitive decline shows a divergent behavior, as presented in a vast multiannual reference study (Schwid et al., 2007), questioning even the utility of using this approach as a valid tool for measuring the clinical impact of medications. Still, MoCA was not included in the mentioned study, thus investigation of its utility in monitoring treatment efficacy is one of the goals of the present study in addition to investigating disease activity and disability evolution during treatment with glatiramer acetate.

MATERIALS AND METHOD

37 RRMS subjects were included, with a short disease course of 3-4 years on average, without any previous disease-modifying therapy. Informed consent was signed by all participants, the study being approved also by the ethics committee of the University of Medicine and Pharmacy "Iuliu Haţieganu", Cluj-Napoca.

Two groups were formed after inclusion, the first referred to as GA (n=23) under glatiramer acetate treatment (20 mg/s.c. for one year) and the second, named NT (n=14), without any disease modifying therapy, receiving placebo instead. Both groups were evaluated for annual relapse rate, EDSS, MSFC and MoCA at inclusion, data marked as GA I or NT I, and after one year of follow-up, presented as GA II and NT II.

Demographic data of the groups are presented in Table I.

Table I. Demographic data – age and sex

		GA	NT
Age		36.67 ± 2.15	37.36 ± 2.05
Sex	M	28.57%	28.57%
	F	71.43%	71.43%

Statistics

Statistical analysis was performed after descriptive statistics and normality testing of the groups, by using the Kolmogorov-Smirnov (K-S) test. Both group sizes and data distribution oriented the analysis towards the use of non-parametric tests, like Kruskal-Wallis (K-W) for independent variables, followed by Mann-Whitney U (M-W) or Wilcoxon (W), using SPSS version 20. Threshold for significance for every test was $p<0.05$.

RESULTS

Annual relapse rate

A non-significant K-W test ($p=0.19$) shows only a tendency for difference between the four sets of data, corresponding to the two groups both at inclusion and at follow-up. The tendency looks more suggestive by consulting Figure 1.

In the next step we tested in a grouped, dependent manner, the presence or absence of differences between the inclusion and follow-up datasets for the two groups. The NT group showed no statistically relevant difference, but in the case of GA treatment, relapse rate was significantly reduced after treatment initiation ($p=0.008$, W).

To complete the analysis, we tested if there are significant differences at inclusion and follow-up between the two groups: no significance was found ($p_{GAIvsNTI}=0.862$ and $p_{GAIIvsNTII}=0.118$, M-W).

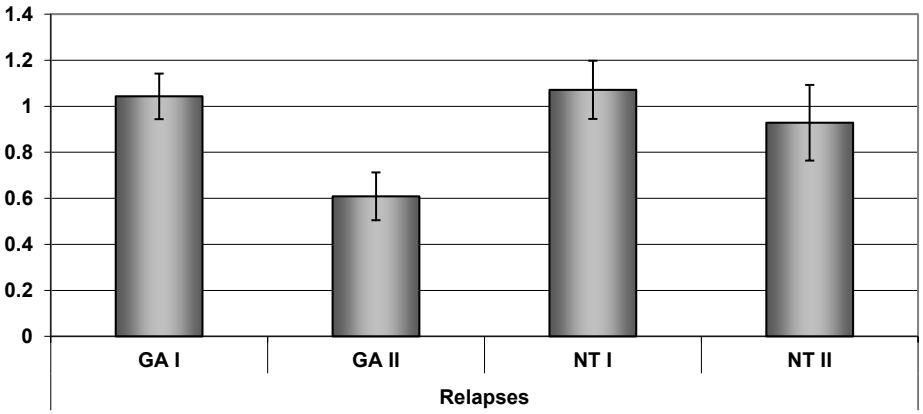

Figure 1. Mean relapse rates of GA and NT groups, both at inclusion and after one year of follow-up

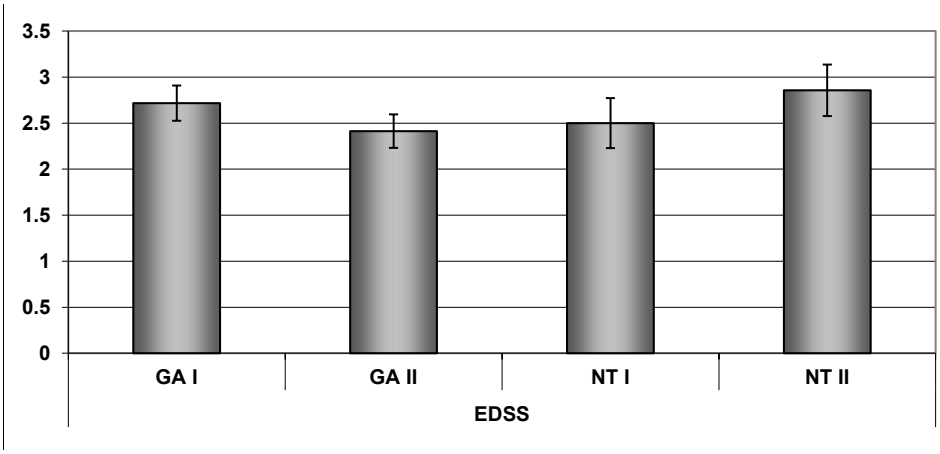

Figure 2. Mean EDSS as compared for NT and GA groups at inclusion and at the one-year follow-up

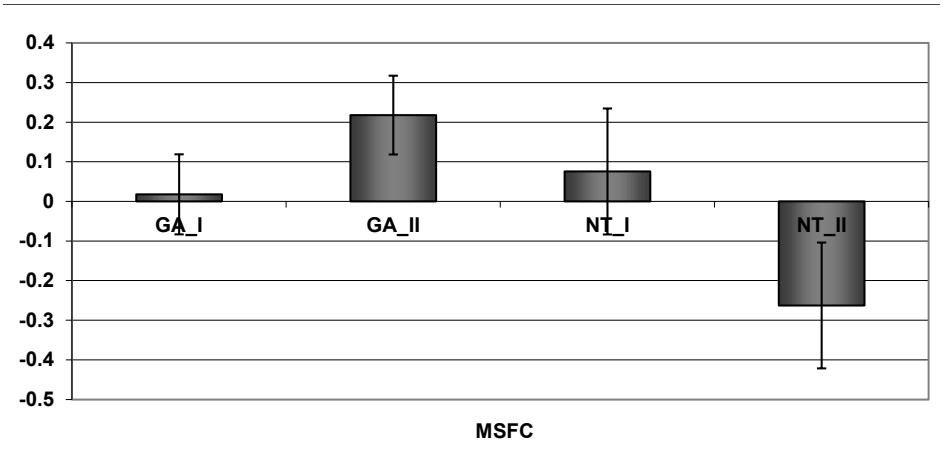

Figure 3. Mean MSFC as compared for NT and GA groups at inclusion and at the one-year follow-up

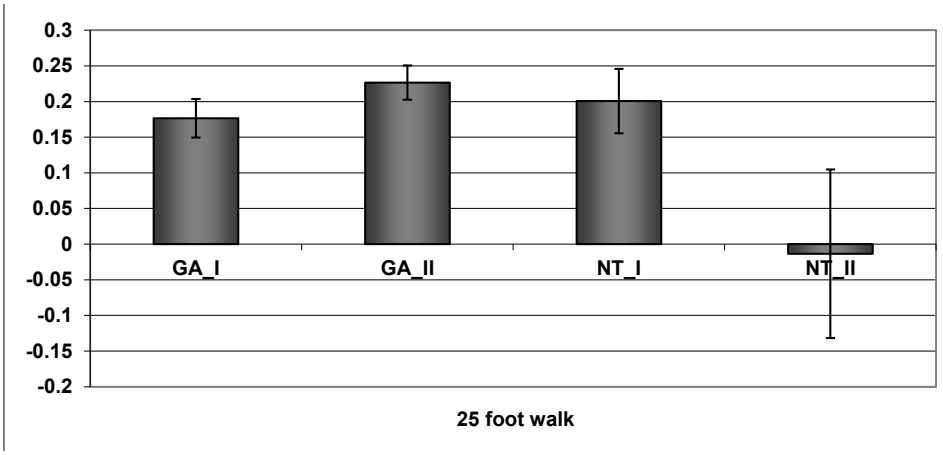

Figure 4. Mean 25-foot-walk score as compared for NT and GA groups at inclusion and at the one-year follow-up

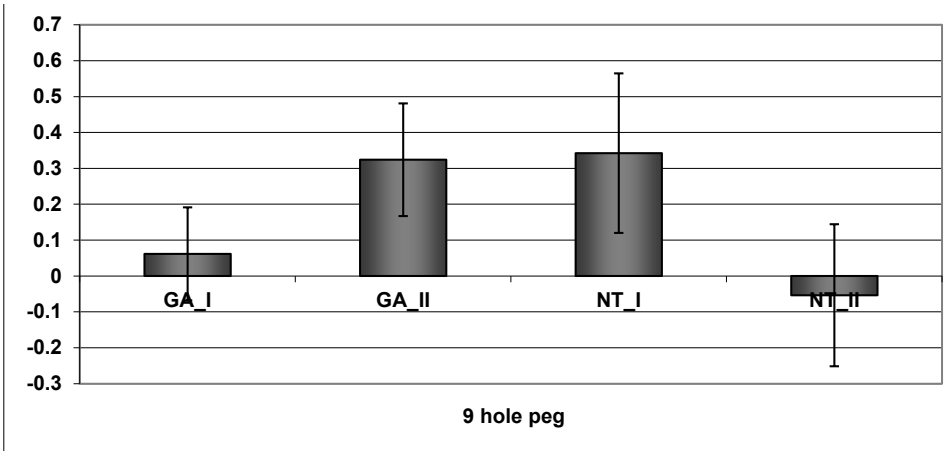

Figure 5. Mean 9-hole-peg score as compared for NT and GA groups at inclusion and at the one-year follow-up

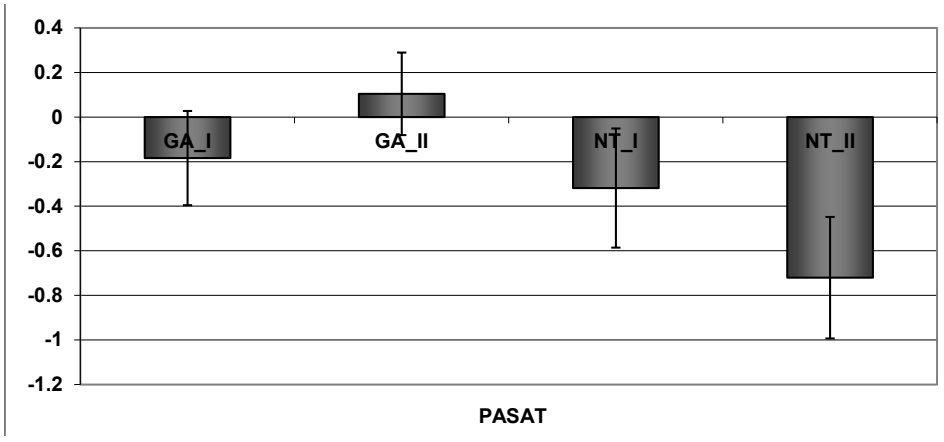

Figure 6. Mean PASAT score as compared for NT and GA groups at inclusion and at the one-year follow-up

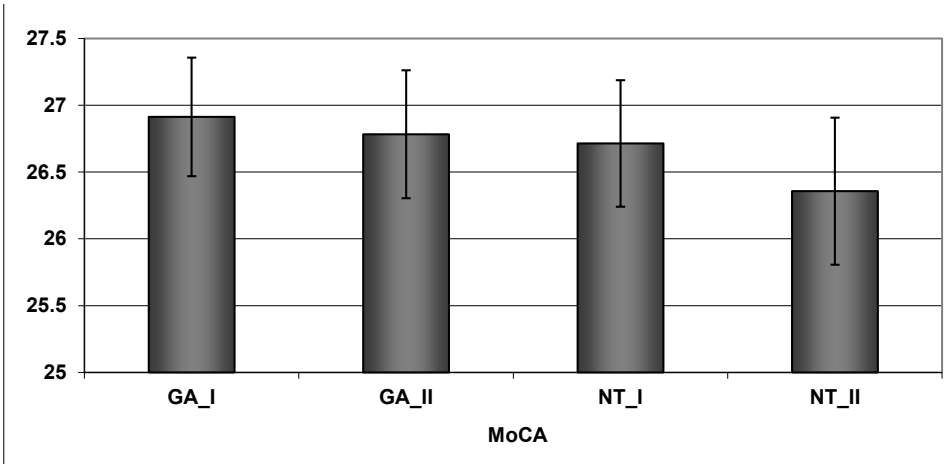

Figure 7. Mean MoCA score as compared for NT and GA groups at inclusion and at the one-year follow-up

EDSS

We used the same testing strategy as above, and no global significance was found (p=0.524, K-W).

Still, highly significant differences were shown for both groups when compared in a pair-wise manner, ($p_{GAIvsGAII}$=0.003, $p_{NTIvsNTII}$=0.008, W), therapy with GA reducing the score, the lack of treatment increasing it.

There were no significant differences though at inclusion and follow-up between the two groups ($p_{GAIvsNTI}$=0.515, $p_{GAIIvsNTII}$=0.215, M-W).

MSFC

Initial test revealed a marginally significant global difference between the four datasets (p=0.067, K-W).

The score was increased in a highly significant manner in case of the treated group ($p_{GAIvsGAII}$=0.0001, W) and dropped with a similar extent in subjects without GA ($p_{NTIvsNTII}$=0.001, W).

To assess equivalence at inclusion we used here also M-W, differences not being relevant ($p_{GAIvsNTI}$=0.684). In the same time follow-up data were tested too, differences being significant here ($p_{GAIIvsNTII}$=0.01).

In the following we present also results for the MSFC subcomponents.

The 25-foot-walk test revealed a relevant global difference (p=0.047, K-W). The score significantly elevated under treatment ($p_{GAIvsGAII}$=0.0001, W), and progressed in a descending manner without treatment ($p_{NTIvsNTII}$=0.002, W).

Groups were comparable at inclusion ($p_{GAIvsNTI}$= 0.481, M-W) but showed relevant differences at follow-up ($p_{GAIIvsNTII}$=0.007, M-W).

Upper limb disability, 9-hole-peg test, had no significant global difference (p=0.235, K-W). Still the score increased importantly under treatment ($p_{GAIvsGAII}$=0.022, W), and dropped in the lack of it ($p_{NTIvsNTII}$=0.001, W).

Inclusion scores were comparable for the groups ($p_{GAIvsNTI}$=0.221, M-W), and there were no significant differences at follow-up ($p_{GAIIvsNTII}$=0.124, M-W).

Cognitive assessment in MSFC was performed by using PASAT. There were no significant global differences (p=0.106, K-W). The score increased under treatment ($p_{GAIvsGAII}$=0.0001, W), and dropped, respectively, without ($p_{NTIvsNTII}$=0.002, W).

Groups were comparable for PASAT at inclusion ($p_{GAIvsNTI}$=0.672, M-W), and showed relevant differences at follow-up ($p_{GAIIvsNTII}$=0.015, M-W).

MoCA

In order to complete cognitive evaluation, groups were tested by using MoCA too, but with no relevant global differences between the datasets (p=0.778, K-W). The one-year reduction of the score under treatment was not relevant ($p_{GAIvsGAII}$=0.083, W), still, the reduction of it without treatment is statistically significant ($p_{NTIvsNTII}$=0.025, W).

Inclusion and follow-up differences between the data were not statistically significant ($p_{GAIvsNTI}$=0.612, $p_{GAIIvsNTII}$=0.419, M-W).

DISCUSSION

As we have mentioned in the introduction, GA has a significant role in the clinical evolution of the RRMS. Our hypothesis was based on the multitude of clinical studies pointing in this direction. The substance, within the years of use, gradually demonstrated that is a feasible evolution modifying option for RRMS, although some of its actions or mechanisms are unclear even today.

Number of relapses and EDSS score were extensively used as measures of therapeutic impact. The treatment with GA showed, in accordance with several studies, a decrease of the number of relapses (Qizilbash et al., 2012, Fernandez-Fernandez et al., 2012) versus the unchanged rate in untreated patients (Johnson 2012), this being impugned as a delay factor in establishing the diagnosis of defined multiple sclerosis (Comi et al., 2008).

In our study, the annual relapse rate showed a significant decrease under treatment with GA, in comparison with untreated patients, in agreement with other similar studies (Martinelli Boneschi et al., 2003, Khan et al., 2001). In this case the observation is appropriate that although the difference is significant, it is pretty reduced, raising the necessity for extending the number of patients included in the study.

The EDSS score rated at inclusion and after one year reveals a significant difference under GA, decreasing the follow-up score towards the moment of beginning the treatment. In this case we can firmly assert the relation: in the case of the non-treated group, we can see a significant increase of the EDSS score within the year of surveillance. Other researchers, using the same score, present similar results (Johnson, 2012). Even from this perspective, we consider the follow-up period as well as the number of included patients insufficient, the increase of the groups and the evaluation period will probably emphasize even more the differences.

In terms of MSFC scale, our results can be divided in three directions. In case of the 25-foot-walk test, the evaluation after one year of GA treatment presents a significant increase of the Z score, meaning that the disability of the lower limbs was reduced under treatment. The difference is more important when faced with the observation that the patients without treatment showed a significant decrease of the score, thus the disability of lower limbs increased.

The Z score shows the same tendencies for the 9-hole-peg test, reflecting an improvement in the function of upper limbs under GA, and a significant increase of hand disability in patients without treatment.

Last, but not least, we present the cognitive component of the MSFC evaluation, the PASAT test. The auditory processing performance was significantly elevated by the disease modifying treatment, and in the case of the NT group, the investigated abilities present a significant decline after one year of evolution.

After the three subcomponents, the MSFC score was calculated, and the statistical analyses were performed. Being a composed marker, it reflects the tendencies of its subcomponents. Thus, in the case of patients treated with GA, MSFC presents a significant increase, this being a reflection of a positive influence of the treatment upon all evaluated functions.

The obtained data presents a convergence with EDSS results, which is actually confirmed by many studies. One of these (Mezei et al., 2006) reveals this convergence even in case of GA treated patients. Regarding MSFC use for evaluation of disease modifying therapies, data from the literature is congruent with our findings (Rossi et al., 2012; Goodin, 2008).

The MoCA test refines the obtained data regarding the treatment's impact on the cognitive capacities. The cognitive decline, reflected through the score's impairment is significant in patients without the modifier treatment and the decrease is not significant under GA treatment. Though, we can report that in case of MoCA test, even if the decrease is not significant, it reveals a tendency towards decline, versus the PASAT test; the difference between these might be explained through a more complete evaluation of the superior cerebral functions in case of MoCA, default a more suitable sensibility of the method for the investigated segments. To define this relationship we even propose the comparative study of the two tests, on different populations with pathologies involving minor cognitive deficits. We also underline that the test was used occasionally, and the present study is one of the first systematic applications in RRMS.

CONCLUSIONS

GA treatment significantly improves the clinical evolution in RRMS, from the point of view of EDSS, MSFC and MoCA scales. The MoCA test can be considered, between the limits of such a short evaluation period, an objective evaluation method of the cognitive function in MS too. The obtained results converge, claiming a possible neuroprotective effect of the drug; presently observed differences would be

expected to be even more significant in the perspective of continuing the study for a longer period and in a larger sample of patients.

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Corresponding author: Major Zoltán Zsigmond, MD, PhD, Dept. of Pharmacology, University of Medicine and Pharmacy "Iuliu Hatieganu", Pasteur 6, 400349 Cluj-Napoca, Romania. Tel/fax: +40-264-595629, +40-740-075796 e-mail: zoltan.major@umfcluj.ro

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A betegség-aktivitás és rokkantság alakulása glatiramer acetát kezelés során. Klinikai megközelítés

Bevezetés: Az irodalom összehasonlító elemzése nyomán megállapítható, hogy glatiramer acetát kezelés alkalmazásakor relapszáló-remittáló szklerózis multiplex esetén megoszlanak a vélemények, de a szerzők többsége jelzi, hogy klinikai szempontból a kezelés pozitív tendenciát mutat. **Célkitűzés/Módszer:** Fő célkitűzésünk kezeletlen és glatiramer acetáttal kezelt betegek összehasonlítása volt, relapszus-előfordulás, Kurtzke's Expanded Disability Status Scale (EDSS) és Multiple Sclerosis Functional Composite (MSFC) mutató – felső végtag és alsó végtag rokkantság és kognitív képességek szempontjából, ugyanakkor a kognitív zavar mérésére Montreal Cognitive Assessment (MoCA) mutató felhasználásával, mindez a glatiramer acetát klinikai hatásának objektív értékelése végett. **Eredmények/Következtetések:** Eredményeink összhangban vannak a mérvadó irodalmi adatokkal egyes módszerek tekintetében – relapszus előfordulás, EDSS, MSFC –, ugyanakkor annak lehetőségét is elővetítik, hogy a MoCA teszt átfogó összehasonlító elemzés után alkalmazható lehet a kognitív funkciók mérésére a gyógyszerhatások elemzése tekintetében szklerózis multiplexben is.

Kulcsszavak: relapszáló-remittáló szklerózis multiplex, EDSS, MSFC, MoCA, glatiramer acetát