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Clinical Data Associated With the Therapeutic Response to Glatiramer Acetate in Multiple Sclerosis Patients

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ABSTRACT

Background: The increasing appearance of new drugs is making more difficult the choice of treatment in multiple sclerosis. According to different criteria, between 20 to 50% of the patients with multiple sclerosis (MS) treated with the classical disease modify treatments (DMT) will have an incomplete response and will need a change for more aggressive therapies. For this reason it is of great importance to improve the selection process in these patients to avoid treatment failures, side-effects and unnecessary risks. The utility of clinical and epidemiological data for the prediction of the therapeutic response to the different MS treatments, and particularly to glatiramer acetate (GA), is insufficient and contradictory.

Objective: To develop a predictive model of clinical data associated with the clinical response to GA.

Methods: Observational retrospective study by reviewing medical charts from October/2002 to February/2012. Data analysis was conducted from February/2014 to February/2015. Inclusion criteria: Relapsing-remitting multiple sclerosis (RRMS McDonald 2010) with ≥1 relapses in the previous 2 years, and ≥2 years of treatment with GA. All the patients included in this study were treated with GA 20 mg injected subcutaneously once daily as the newer formulation of GA 40 mg 3 times weekly was not approved at the time of the study. Definitions: Responders: ≤1 relapse and no disability progression; Non-responders: ≥2 relapses and/or disability progression. Disability progression: EDSS increase ≥1.5 points if basal EDSS=0; increase ≥1 if basal EDSS=1-5; increase ≥0.5 if basal EDSS ≥5.5. Statistical analysis: logistic regression. Association variable: odds ratio.

Results: Two hundred and four subjects included. Responders: 137 (67.5%). Number of relapses in the 2 years before GA onset was associated with a worse clinical response (odds ratio (OR): 1.4; IC 95%: 1.12-1.74%). Accuracy of this model (AUC: 63.5%; IC 95%: 56.2-70.7%); Diagnostic parameters: Sensitivity: 40%; specificity: 79.8%, positive predictive value: 78.6; negative predictive value: 41.7.

Conclusions: GA was associated with a better response in Relapsing-remitting multiple sclerosis (RRMS) patients with low-moderate disease activity. This model could be improved incorporating serological, genetic and imaging data.

KEYWORDS: Multiple sclerosis; Glatiramer acetate; Clinical response; Predictive factors.

ABBREVIATIONS: MS: Multiple Sclerosis; CNS: Central Nervous System; DMT: Disease Modify Treatments; GA: Glatiramer Acetate; MBP: Myelin Basic Protein.

INTRODUCTION

Multiple sclerosis (MS) is a demyelinating and neurodegenerative disease of the central nervous system (CNS) that affects a high number of patients in the western world and represents the 2nd cause of disability in young people of these countries.[1,2]

Its causes are not completely understood, but it is accepted that it has a multifactorial origin, with environmental and genetic factors playing a role and then autoimmune and neurodegenerative mechanisms against the myelin sheath.[3]

Over the last years, we are witnessing a great progress in the treatment of multiple sclerosis (MS). Currently there are 10 therapies approved for this disease, and this number is going to increase in the near future with other several drugs in the last stages of their clinical trials, making more difficult to choose the best treatment for each individual patient.

According to different criteria, between 20 to 50% of the patients with MS treated with the classical disease modify treatments (DMT) will have an incomplete response,[4-6] and will need a change in their therapy. In this scenario, it is becoming more important to develop tools that allow an earlier prediction of the clinical response, and improve the therapeutic election, by avoiding therapeutic failures of first-line treatments or unnecessary risks from more aggressive drugs.

The glatiramer acetate (GA) is a classic immunomodulator which consists of a mix of oligopeptides of 4 amino-acids that resembles the myelin basic protein (MBP),[7,8] and with a well documented efficacy and tolerability both at short and long-term.[9-16] Recently it has been approved a new formulation of 40 mg which is given with subcutaneous injections 3-times weekly, instead the previous 20 mg once-daily, with the same efficacy and safety profile.[17,18]

The objective of this study is to build a predictive model of clinical data associated with the clinical response to GA, to improve the treatment selection in patients with MS.

MATERIAL AND METHODS

Design and Study Population

Retrospective and observational study by reviewing the medical charts of the patients attending to the demyelinating diseases unit of the Clinico San Carlos Hospital (HCSC) (Madrid, Spain), from October, 2002 to February, 2012. Data analysis was conducted from February, 2014 to February, 2015.

We included all the patients with the diagnosis of relapsing-remitting multiple sclerosis (RRMS),[19] with at least 1 relapse in the last 2 years before the initiation of GA, and who had received treatment with GA for a minimum of 2 years. Those patients who suspended GA before 2 years of therapy due to early clinical failure were also included. All the patients included in this study were treated with GA 20 mg injected subcutaneously once daily as the newer formulation of GA 40 mg 3 times weekly was not approved at the time of the study.

We analyzed the variables: sex, age at onset of MS, previous treatments, age at onset of GA, number of relapses in the 2 years before GA, number of relapses during the study, basal expanded disability status scale (EDSS), and EDSS every 6 months.

The patients gave their written consent to participate in this study. The research fulfilled with all the Helsinki declaration requirements, and was approved by the ethics committee of the HCSC. The results of the study are completely confidential complying with all the legal steps established in the 1999 Spanish data protection law.

Definitions

We considered responder (R) those patients with no more than 1 relapse and without disability progression (DP), and non-responder (NR) those patients with ≥2 relapses and/or DP. Patients who withdrew GA before 2 years due to early clinical failure were also classified as NR.

We defined DP as an increase in the EDSS of ≥1.5 points if basal EDSS=0; ≥1 if basal EDSS=1-5; and ≥0.5 if basal EDSS ≥5.5.

These criteria were chosen because their wide use in the majority of other studies, and to optimize the detection of clinically significant associations, and therefore their applicability in the routine daily practice.[10,11,20,21]

Statistics

The statistical analysis was done using the IBM© SPSS Statistics® software for windows, version 19.

The study of the association between the clinical data and the therapeutic response to GA was done with binary logistic regression. We used the odds ratio (OR) as the association variable.

The calibration of the model was studied using the Hosmer and Lemeshow test for goodness of fit.

The accuracy of the model was calculated using the area under the curve (AUC) with receiver operating characteristic (ROC) models. The sensitivity (SE) and specificity (SP) were estimated with the regression model. The positive predictive

value (PPV) and the negative predictive value (NPV) were estimated using the Baye's theorem with the macro! DT for IBM© SPSS® Statistics software.[22]

The statistical significance was established at *p*<0.05 for all of the statistical tests.

RESULTS

Two hundred and four patients were included. One hundred and seventy eight completed at least 2 years of GA, and 26 were included as early treatment failure.

There were 139 women (68%) and 65 men (32%). The mean age at diagnosis of MS was 30.8 years (SD±9.01), and the mean age at onset of GA was 35.9 years (SD±9.2). The mean basal EDSS was 1.8 (SD±1.03) and the mean number of relapses in the previous 2 years was 2.1 (SD± 1.4). One hundred and fifty six (76.5%) out of the 204 patients were using GA as their 1st therapeutic option, and 23.5% (48) as second line treatment after immunosuppressants or interferon beta (IFN-b) failure.

There were 137 responders. This represented a proportion of response of 67.5% (IC 95%: 61-74%).

Number of relapses in the previous 2 years before the initiation of GA was associated with the probability of response to GA. The rest of variables were not statistically associated (Table 1).

Each relapse in the previous 2 years before GA onset increased the risk for lack of response to GA in 1.4 (IC 95%: 1.12-1.74; *p*=0.003). Age of onset of MS showed a trend to a better response in older patients, but without achieving statistical

significance (OR: 0.96; *p*=0.051). This could be due to less aggressive disease in older patients as inflammatory component of MS and relapses tend to decrease with time.

The calibration of the model was excellent without statistically significant differences between the predictions and the real results (chi-square=1.64, *p*=0.89).

The accuracy of the model was moderate, with a proportion of correct predictions of 64.7% (IC 95%: 55-74.5%). Using ROC curves to determine the best threshold to classify responders, we chose a probability of response of ≥70%. This value yielded a low sensitivity (42.7%) but with a good specificity (79.2%). With the percentage of response previously obtained in our study and these diagnostic values, we would have the following positive and negative predictive values (Table 2).

Combining the number of relapses and the basal-EDSS in a prognostic table, the probability of response to GA would be the following (Table 3).

DISCUSSION

The utility of clinical and epidemiological data for the prediction of the therapeutic response to the different MS treatments, and particularly to GA, is insufficient and contradictory.

On the one hand, the first clinical trials of GA showed a trend to fewer relapses in those patients with lower basal EDSS,[9-11] and a meta-analysis of the 3 pivotal trials of GA found that the starting EDSS and the number of attacks during the last 2 years were predictive factors of relapses.[23] In the same way, some observational studies did also describe such predictive factors. One of these researches, conducted on 272 patients to assess the

Variable	OR for GA failure	CI 95%	*p*
Sex	0,97	0,54-1,74	*p*=0,92
Age at MS onset	0,96	0,93-1	*p*=0,051
Age at GA onset	1,02	0,97-1,08	*p*=0,38
GA 1st line VS 2nd line	1,23	0,66-2,54	*p*=0,45
Basal EDSS	1,05	0,79-1,39	*p*=0,73
Nº relapses last year	1,19	0,77-1,84	*p*=0,43
Nº relapses 2 last years	1,33	1,09-1,63	*p*=0,003[*]

GA: Glatiramer acetate; MS: Multiple sclerosis; EDSS: Expanded disability status scale; OR: Odds Ratio; CI: Confidence interval; *p*: *p* value.

Table 1: Association between clinical variables and clinical response to glatiramer acetate.

Hypothetical prevalence	Positive predictive value	Negative predictive value
58%	73,9%	50%
65%	79,2%	42,7%
70%	82,7%	37,2%

Table 2: Diagnostic values of the logistic regression model.

Basal EDSS	Nº of relapses in the last 2 years					
	1	2	3	4	5	6
0	82,1%	77,1%	71,2%	64,5%	57,2%	49,5%
1	78,6%	73,1%	66,5%	59,4%	51,8%	46,1%
1,5	76,8%	70,8%	64,1%	56,7%	49,1%	41,5%
2	74,8%	68,5%	61,6%	54,1%	46,4%	38,9%
2,5	72,7%	66,2%	59%	51,4%	43,7%	36,3%
3	70,5%	63,7%	56,3%	48,6%	41,1%	33,8%
3,5	68,2%	61,1%	53,6%	45,9%	38,3%	31,5%
4	65,8%	58,5%	50,9%	43,3%	35,9%	29,2%
4,5	63,3%	55,9%	48,2%	40,6%	33,5%	27%
5	60,7%	53,2%	45,5%	38%	31,1%	24,9%
5,5	58,2%	50,5%	42,8%	35,5%	28,8%	22,9%
6	55,5%	47,8%	40,2%	33,1%	26,7%	21,1%

Table 3: Probability of response to glatiramer acetate in relapsing remitting multiple sclerosis patients using the number of relapses in the last 2 years and the basal-EDSS as predictors.

response to IFN-b and GA, found that older age at diagnosis, lower basal EDSS and less Magnetic resonance imaging (MRI) activity, increased the probability of response to the treatment.[24]

On the other hand, other studies do not share these findings. In a big observational study carried out in our country, the researchers did not find any epidemiological variable (sex, age at MS onset, duration of MS, and duration of GA treatment), nor clinical factors (number of relapses in the last year, basal EDSS and previous failure of IFN-b) significantly associated with the likelihood of attacks or disability progression.[25] Other observational study developed in Brazil did not meet any significant association either.[26]

It is clear that all these differences have to be related with methodological issues, but it is reasonable to expect a better response in those patients with milder MS.

Our work represents a large sample of 204 patients, with a good calibration of the regression logistic model, and therefore with a reliable internal validity of the results. Moreover, our study was conducted in only one center, yielding a greater homogeneity in the interpretation of the clinical data, and therefore with a greater internal validity. Finally, the epidemiological data of our sample are very similar to other previous series,[25-27] with comparable sex ratios, average age at onset of MS and average basal EDSS and annualized relapse rate. Beside this, it represents a meaningful variety of conditions that resemble very well the real life situations of the daily clinical practice.

In our study, we found an association between the number of relapses during the previous 2 years before the initiation of GA and the probability of response. These data would be in line with the results of the first clinical trials and their meta-analysis,[9-11,23] and some observational studies mentioned before,[24] in which older age, lower basal EDSS, lower relapse rate and less MRI activity were associated with the probability

of response to GA.

We have to keep in mind that the overall diagnostic accuracy of the model was only moderate (64.7%; IC 95%: 55-74.5%) and the negative predictive value was low (37.2-50%). But the positive predictive value was good (73.9-82.7%). This means that with this model, we would lose some patients predicted to be non-responders and who could have had a good evolution with GA. But those patients predicted to be responders to GA would benefit from this treatment with a low risk of failure.

As previously described, if we settle a threshold of probability of response ≥70% to consider one patient as a good candidate to receive treatment with GA, this drug would be effective in RRMS patients ranging from basal EDSS=0 and a maximum of 2 relapses during the last 2 years, to EDSS=3.0 and only 1 relapse. These criteria would be achieved by 34.5% (IC 95%: 28.6-40.5%) of our sample. We chose this threshold of 70% because of its statistical performance according to the ROC curves, as there are not many other studies with this methodology.

For all these reasons, we think that this algorithm could be easy and useful to apply in the daily clinical practice, and with a low risk of error in a patient predicted to be responder.

CONCLUSION

The results of this study support the hypothesis that the less severe MS patients would have more opportunities to have a good response to GA. We were able to develop a predictive model of response to this treatment with the variables number of relapses during the last 2 years of disease and basal EDSS. We think that this model could be useful and applicable in the daily clinical practice. Nevertheless, it would be necessary to improve this predictive model with the incorporation of new variables like blood, genetic, serological and/or MRI biomarkers, to get more

statistical power and better results of the diagnostic parameters.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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