

IMMUNOMODULATOR THERAPY MIGRATION IN RELAPSING REMITTING MULTIPLE SCLEROSIS

A study of 152 cases

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Abstract – Background: Since 1997, immunological modulators have been used for treatment of Relapsing Remitting Multiple Sclerosis (RRMS) in the Multiple Sclerosis Attendance and Treatment Center (CATEM) with significant alterations in this disease natural history. **Aim:** To add data on the experience of CATEM for the treatment of RRMS patients that had immunomodulators. **Method:** RRMS patients that received continuously immunomodulator drugs were evaluated on adherence, migration, withdrawal and progression rates. The patients were divided in three groups by the period of immunomodulators intake. **Results:** There were registered in Group 1 withdrawal in 98 patients (25%) and adherence in 292 cases (74%); Group 2 interruption of therapy in 140 patients, 92 (31%) due to progression for PSMS, 14 (5%) for pregnancy, withdrawal in 34 (11%), adherence in 88%; Group 3 progression in 41 (26%), pregnancy in 3 (2%) withdrawal in 42 (27%) and adherence in 72%. The migration rate was about one third (31.57%) and the principal cause was therapeutic failure; the mean migrating time was 0.5-2.5 years in group 3. **Conclusion:** Immunomodulatory treatment for RRMS patients may have significant levels of failure and side effects; the adherence was compatible with the international literature.

KEY WORDS: multiple sclerosis, treatment, immunomodulators, adherence, migration, withdrawal.

Migração medicamentosa de imunomoduladores em esclerose múltipla: estudo em 152 pacientes

Resumo – Introdução: Na última década foram introduzidos os imunomoduladores para o tratamento da esclerose múltipla (EM) forma remitente-recorrente (RR). **Objetivo:** Complementar o relato anterior da experiência de centro brasileiro no acompanhamento dos pacientes em uso dos imunomoduladores. **Método:** 390 pacientes que faziam uso de imunomoduladores no Centro de Atendimento à Esclerose Múltipla (CATEM), foram subdivididos por tempo de uso em três grupos, avaliando-se as ocorrências de: abandono, gravidez, conversão da forma RR para secundária progressiva (SP) e da aderência. **Resultados:** No Grupo 1, foram observados abandono do uso de imunomoduladores em 98 pacientes (25%) e aderência de 292 casos (74%); no Grupo 2, interrupção da medicação, no total de 140 pacientes, 92 (31%) por conversão para a forma SP, 14 (5%) por gravidez e 34 (11%) por abandono, mantendo a aderência em 88% dos demais pacientes; no Grupo 3, conversão em 41 (26%) dos casos, gravidez em 3 (2%) e abandono em 42 (27%). A aderência se manteve em 72%. O índice de migração foi de quase um terço (31,57%), no grupo 3, tendo como principais causas: a falha terapêutica e efeitos colaterais realizando-se a migração do imunomodulador em 0,5–2,5 anos. **Conclusão:** A percentagem de abandono observada é compatível com os dados encontrados na literatura mundial.

PALAVRAS-CHAVE: esclerose múltipla, tratamento, imunomoduladores, aderência, migração, abandono.

Multiple sclerosis (MS) is an autoimmune disease with demyelinating¹ inflammatory features which attacks young adults between 20 and 40 years old more often, it is a frequent cause for neurological disability at this age group². In our environment the estimated prevalence is 15:100000². It is more common in white people, and it is frequent in temperate climate areas. It has high prevalence in

Great Britain, Scandinavia, north of the United States and Canada. It is the most common cause for long time neurological disability in young adults¹⁻⁵. Although it is not direct inherited, MS usually attacks susceptible people who seem to be more sensitive to certain stimulus or agents. There is no available treatment which can completely interrupt disability increase⁶.

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Since the last decade immunomodulators have been introduced for Relapsing Remitting MS (RRMS) treatment. There are two kinds of interferon beta: 1a – Rebif® dispensed subcutaneously⁷, and Avonex® dispensed intramuscularly⁸ and 1b – Betaferon®⁹ and Glatiramer Acetate Copaxone®, both dispensed subcutaneously. Immunomodulators are drugs which modify the disease natural course (disease-modifying drugs) reducing its activity, delaying the disability progress¹⁰⁻¹⁴, and also reducing treatment costs. Nevertheless, there are not many studies comparing immunomodulators.

This study aimed to complement the Brazilian center previous report³ on the experience with patients using these drugs evaluating the rates of immunomodulatory drugs migration at CATEM.

METHOD

From April,1997 to December, 2004 the Multiple Sclerosis Attendance and Treatment Center (CATEM) admitted patients with defined diagnosis according to Poser et al.¹⁵ criteria. Three hundred ninety patients who used immunomodulators were selected among them and they were divided in three groups, according to the continuous use of the drugs: Group 1 – up to 2 years use (390 cases); Group 2 – from at least 2 years to 3 years use (292 cases); Group 3 – from 3 to 5 years use (152 cases).

We evaluated the occurrence of: withdrawal, pregnancy, conversion from RR kind to PSMS and adherence in the three groups. The causes for migration and withdrawal were evaluated in Group 3.

A retrospective cohort study was held in Group 3, reviewing all MS in the Attendance and Treatment Centre (CATEM) patients' reports. 152 are RRMS patients⁹ receiving immunomodulators. We stated as a therapeutic failure the EDSS (expanded disability status score) increase by one point from the patient's initial disability which was sustained for six months^{13,16-18}, associated or not with the number of outbreaks increase (more outbreaks per year in comparison with the previous rate of outbreaks).

Inclusion criteria: patients with the RRMS continuously receiving the immunomodulator; who had their immunomodulator changed.

Exclusion criteria: progression to progressive secondary MS (PSMS); migration insufficiently documented or done by other medical service; migration due to pregnancy.

After analysing the inclusion/exclusion criteria, 152 patients' reports receiving drugs regularly until November, 2005 were re-

viewed. We considered: EDSS in the beginning of treatment with immunomodulator; the time spent, in years, until their migration; EDSS at the migration moment; the cause for migration: 1-EDSS increase, 2-side effects, 3-increase in outbreaks number

This study was approved by the institution ethics commission.

RESULTS

In Group 1 we observed withdrawal in the use of immunomodulators in 98 patients (25%). We did not register any case of conversion from RR kind to SPMS and any case of pregnancy during this period, but we observed adherence in 292 cases (75%) (Table 1).

In Group 2 we observed medication interruption in 140 patients, in 92 (31%) because of conversion to SPMS,

Table 1. Immunomodulators used in group 1, 2 and 3.

	Group 1	Group 2	Group 3
Patients number	390	292	152
Pregnancy	0	14 (5%)	3 (2%)
Conversion	0	92 (31%)	41 (26%)
Withdrawal	98 (25%)	35 (11%)	42 (27%)
Adherence	92 (75%)	258 (88%)	110 (72%)

Table 2. Migration rate: immunomodulator and mean time: migration rate because of immunomodulator and migration mean time.

Immunomodulator	Migration rate	Mean time for migration
INFβ 1a SC	24 (50%)	2.5 years
INFβ 1b SC	14 (25%)	1.9 years
INFβ 1a IM	9 (18.75%)	2.1 years
A. Glatir	1 (2.08%)	0.5 years

Table 3. Causes for general migration by period of immunomodulator receiving.

Cause for migration	Patients	Mean time
EDSS increase	29 (60.4%)	2.61 years
Outbreaks increase	18 (37.5%)	2.42 years
Side effects	18 (37.5%)	1.69 years

EDSS, expanded disability status score.

Table 4. Reasons for migration because of immunomodulator.

Immunomodulator	EDSS increase	Outbreak increase	Side effects	Others
INFβ 1a SC	15 (62.5%)	08 (33.3%)	11 (45.8%)	
INFβ 1b SC	8 (57.1%)	6 (42.8%)	4 (28.5%)	2 (14.28%)
INFβ 1a IM	6 (66.6%)	4 (44.4%)	2 (22.2%)	
A. Glatir			1 (100%)	

in 14 (5%) because of pregnancy and in 34 (11%) because of withdrawal, keeping adherence in 88% of the other patients (Table 1).

In Group 3 there was conversion in 41 (26%) of the cases, pregnancy in 3 (2%) and withdrawal in 42 (27%). Adherence was kept in 72% (Table 1).

From 152 patients selected according to the inclusion/exclusion criteria, in Group 3, the patients who did not migrate from medication until the moment of the cohort were not evaluated in this study.

Forty eight (31.57% – total migration rate) migrations from medication were registered, among them 24 (50%) were from INFβ 1a SC to another immunomodulator: 14 (25%) from INFβ 1b SC, 9 (18.75%) from INFβ 1a IM and 1 (2.08%) from A. Glatir. The mean time spent from the treatment beginning with an immunomodulator until its change was of 1.77 years, and for INFβ 1a SC it was of 2.5 years, INFβ 1b SC 1.95 years, A. Glatir 0.5 years and INFβ 1a IM 2.13 years (Table 2).

Among the causes for general migration by period of immunomodulator receiving, 29 patients (60.4%) migrated due to EDSS increase with mean time of 2.61 years; 18 (37.5%) due to the outbreaks increase in mean time of 2.42 years; 18 (37.5%) due to interferons side effects with mean time of 1.69 years (the patient may have migrated for more than one reason) (Table 3).

The causes for migration due to immunomodulator from INFβ 1a SC concerned: 15 (62.5%) due to EDSS increase; 11 (45.8%); side effects; and 8 (33.3%) increase in the number of outbreaks. The causes for migration from INFβ 1b SC concerned: 8 (57.1%) due to EDSS increase; 4 (28.5%) due to side effects and 6 (42.8%) due to increase in the number of outbreaks. The causes for migration from INFβ 1a IM concerned: 6 (66.6%) due to EDSS increase; 2 (22.2%) due to side effects and 4 (44.4%) due to increase in the number of outbreaks. Only one change due to side effects (100%), was the cause for migration from A. Glatir (Table 4).

DISCUSSION

In Group 3, almost one third (31.57%) of RR patients who migrated from immunomodulator showed a migration rate almost 10% bigger than the one found by Morrà et al.¹⁹ (20.4%), with change mean time of 24 (±17) months, while in our study it was of 1.77 years (19 months) average. Most of the changes had the disability increase as a main cause. Side effects and increase in the number of outbreaks had the same rate, the second cause reflecting the partial response to treatment with immunomodulators. Lyseng-Williamson and Plosker²⁰ reported that INFβ 1a should be the first choice for the treatment of the RRMS and that INFβ 1a SC (Rebif®) would be more efficient in reducing

the outbreaks number and side effects when compared to INFβ 1a IM (Avonex®). But Haas and Firzlafl¹¹ showed that A. Glatir. significantly reduced outbreaks number when compared to interferons and also showed that adherence to A. Glatir. was bigger than to interferons, in a period of 24 months. Vallitu et al.¹⁴, reported in their paper that A. Glatir. is as efficient as the interferons and must be a good option for migration due to intolerance and therapeutic failure concerning interferons⁵. Carra et al.²¹ also showed A. Glatir. bigger effectiveness in reducing the number of outbreaks when compared to interferons, but they did not observe any difference in the disability evolution.

In Group 3, the number of patients using INFβ 1a SC and A. Glatir. is alike, followed by INFβ 1b SC, which represents a higher number of patients using it at CATEM. INFβ 1a IM is the least used immunomodulator in the clinic, but it is the cause for almost 20% of total migrations, and it agrees with what Lyseng-Williamson and Plosker²⁰ reported concerning a bigger number of side effects related to the use of INFβ 1a IM.

Migration due to side effects happened earlier (1.69 years) than the other reasons (EDSS increase 2.61 years and increase in the number of outbreaks 2.42 years) considering the first medication.

INFβ 1a SC had the highest number of migrations followed by INFβ 1b SC, INFβ 1a IM and A. Glatir., this one showed only one case of migration due to side effects suggesting that it could be the most efficient immunomodulator. As INFβ 1a SC and INFβ 1b SC were introduced in 1997 and INFβ 1a IM and A. Glatir. in 2001, we can not state that A. Glatir. should be more efficient than the interferons.

In our study the rate of immunomodulators withdrawal up to 3 years was 34%, O'Rourke and Hutchinson (Ireland)²² found 28% while the Italian study²³ was 41% and in the Canadian study²⁴ it was 39%, during the same three years.

According to O'Rourke and Hutchinson²² study the therapeutic failure is an important cause for withdrawal in the second year of treatment, and we also observe this fact in our study.

In the Irish study withdrawal causes had the same rates for side effects and therapeutic failure. The Canadian study observed 30% withdrawal due to therapeutic failure, 70% due to side effects. In our study withdrawal causes were 19% due to the disease failure/progression and 14% due to side effects in groups from 3 to 5 years.

In short, the migration rate was of almost one third (31.57%), and that the main causes were: therapeutic failure and side effects. It can not be suggested that some immunomodulator may be more efficient for the treat-

ment of RRMS (at least in this sample), so it needs more studies to be proved. One third of the patients at CATEM had therapeutic failure which was detected and caused migration from immunomodulator in 0.5–2.5 years. Migration occurred earlier (1.69 years) when it happened due to side effects. The observed withdrawal rate in our paper is compatible to the data found in the international literature and it suggests that the treatment of multiple sclerosis still has a considerable therapeutic failure rate.

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