IMMUNOMODULATORY TREATMENT IN MULTIPLE SCLEROSIS

Experience at a Brazilian center with 390 patients

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ABSTRACT - Since 1993 the Federal Drug Administration approved the use of immunomodulatory therapy in multiple sclerosis (MS), modifying the natural course of disease, as demonstrate our experience in t reatment of MS patients at the MS Treatment Center (CATEM).   *Objective:* To evaluate patient behavior using immunomodulatory therapy for a period of five years treatment.   *Method:* We selected 390 patients in CATEM with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) with relapses.   *Results:* At initial treatment 292 (61.5%) patients presented RRMS, 98 (20.6%) SPMS with relapses, 27 SPMS (5.6%) and 58 (12.1%) primary progressive MS (PPMS). In RRMS 182 (62.5%) used the interferon β 1a SC, 15 (5.2%) interferon β 1a IM, 85 (29%) interferon β 1b and 10 (3.3%) glatiramer acetate. In SPMS 63 (64.3%) used interferon β 1a SC, 4 (4.1%) interferon β 1a IM and 31 (31.4%) interferon β 1b. We observed that in this period 195 (50%) migrated between drugs, 35 (9%) gave up therapy and 160 (41%) continued the initial therapy.   *Conclusion:* Stopping the immunomodulatory therapy emerges as a problem in the second year of treatment and it can be a subset of interferon non responsive or development of neutralizing antibodies.

KEY WORDS: multiple sclerosis, immunomodulatory therapy, treatment failure.

Tratamento imunomodulador na esclerose múltipla: experiência em um centro brasileiro com 390 pacientes

RESUMO - A partir de 1993, com a aprovação pela Federal Drug Administration (FDA) do uso de imunomoduladores na esclerose múltipla (EM), houve alterações significativas na história natural da doença.   *Objetivo:* Avaliar o comportamento dos pacientes com uso de imunomoduladores no decorrer de 5 anos. *Método:* Foram atendidos 589 pacientes no CATEM, sendo selecionados 475 pacientes e excluídos os portadores das f ormas progressiva secundária sem surtos (PS) e progressiva primária (PP).   *Resultados:* No início do tratamento 292 (61,5%) pacientes apresentavam a forma RR, 98 (20,6%) forma PSS, 27 PS (5,6%) e 58 (12,1%) PP. Na forma EMRR 182 (62,5%) utilizaram o interferon β 1a SC 3x/semana, 15 (5,2%) interferon β 1a IM 1x/semana, 85 (29%) interferon β 1b e 10 (3,3%) acetato de glatiramer; na forma EMSP 63 (64,3%) utilizaram o interferon β 1a SC, 4 (4,1%) interferon β 1a IM e 31 (31,4%) interferon β 1b. 35 (9%) pacientes pararam de utilizar a medicação, 195 (50%) migraram entre imunomoduladores e 160 (41%) pacientes continuaram usando o imunomodulador inicial.   *Conclusão:* Não tivemos a intenção de comparar os interferons β a fim de demonstrar qual o melhor ou qual teve maior falência. Contudo, é fato que o risco de falência das medicações a partir do segundo ano de tratamento ocorre e pode ser por pacientes não responsivos aos interferons β ou ao surgimento dos anticorpos neutralizantes.

PALAVRAS-CHAVE: esclerose múltipla, terapia imunomoduladora, falha terapêutica.

Since 1993, the Federal Drug Administration (FDA) a p p roved the use of immunomodulatory therapy in multiple sclerosis (MS), modifying the natural course of disease[1]. In 1997, and after in 2001, The Health Department approved this medicine for the use in our enviroment[2], modifying as from those dates the course of MS in Brazil. In the city of São Paulo the prevalence of MS is 15/100000 inhabitants[3]. In April

of 1997 the Assistant Center and Treatment of MS (CATEM) of the Neurology Discipline of the University of Medical Science Santa Casa of São Paulo was created. Since then, patients with MS have been evaluated and included in the protocol treatment with immunomodulators[1]. MS is an inflammatory demyelinating disease of the Central Nervous System (CNS) more frequent in North America and North of Europe[4]. The disease is the result of aggression of the myelin shaft in the CNS, causing oligo and axonal lesion. Provoking young adult's age between 20 and 40 years old, causing incapacity in more than 50% of the patients[5]. The etiology of the disease is still unknown and the symptoms vary depending on the lesion localization, the most commom are: sensitive symptom, sphincter dysfunction, optical neuritis, ataxia, diplopia and the pyramidal motor deficit[5]. MS can develop in several ways: recurring-remittent way (RRMS), pro g ressive secondary way (SPMS) with and without outbreaks and primary pro g ressive (PPMS)[6].

Interferon β was the first drug to demonstrate immunomodulatory quality, followed by glatiramer acetate, as it controls more specifically the dere g ulation of the present immune system in MS[7-9] and the studies demonstrate yet direct effects related to outbreaks and the appearance of incapacities[4,10,11].

The objective of this study is to evaluate patient's behavior with the use of immunomodulators durind 5 years. The efficiency os the established drugs has not been analyzed.

METHOD
589 patients were attended at CATEM and 475 patients were selected with defined diagnosis of M S according to criteria of Poser et al.[12], between May of 1997 and June 2003 (1 year/5 years). Patients are attended at CATEM with inconclusive diagnosis from several places of São Paulo and Brasil that are attended through appointments for the diagnosis confirmation, behavior and future follow-up. This g roup (475) included patients of both genders, with age between 18 and 50 years old and classified by the Lubling et al.[6] criteria in RRMS way, secondary progressive with outb reaks (SPSMS), SPMS without outbreaks and PPMS, being 292 RRMS, 98 cases SPSMS, 27 SPMS and 58 PPMS.

The patients were oriented to use immunomodulators according to standards and guidelines of the Health Department in accordance with the clinical forms, degree of functional incapacity, presence of other associated diseases[1,2].

We submitted the patients to neurological evaluation every six months. Degree of functional incapacity, presence of adverse side effects, suspensi on of drugs, disease progression or treatment abandon were noted, 85 (14.4%) patients were excluded. They were bearers of SPMS and PPMS type without outbreaks (as they did not use immunomodulators), 114 patients (19.3%) that did not p resent MS or those that had incomplete re c o rds or that abandoned the treatment before a period of one year.

RESULTS
Results are summarized in Tables 1 to 5.

During initial treatment 292 patients (61.5%) presented RRMS type, 98 (20.6%) SPSMS, 27 SPMS (5.6%) and 58 (12.1%) PPMS. Average age at the diagnosis was 31.3 in RRMS type, 37.5 SPMS and 43.3 in PPMS type years old. Type RRMS revealed 25% male sex and 75% female. SPMS 27% male and 73% female and in PPMS type 86% female and 14% male.

The majority of the 390 patients (82.1%) started treatment with immunomolators and the main adverse effects were skin allergy reaction, shivers, fever, myalgias, being transitory and that occurred

Table 1. Patients that started the use of immunomodulator.

Clinical form	Interferon β 1a SC (n=245/%)	Interferon β 1a IM (n=19/%)	Interferon β 1b (n=116/%)	Glatiramer acetate (n=10/%)	Total (n=390)
EMRR	182/ 46%	15/ 3.8%	85/ 21.8%	10/ 2.5%	292
EMSP	63/ 16.1%	04/ 1%	31/ 8%	0	98

EMRR, multiple sclerosis recurring-remittent; EMSP, multiple sclerosis secondary progressive.

Table 2. Patients that stopped using of immunomodulators.

Clinical form	Interferon β 1a SC (n=25/%)	Interferon β 1a IM (n=2/%)	Interferon β 1b (n=8/%)	Total (n=35)
EMRR	08/ 2%	02/ 0.5%	02/ 0.5%	12
EMSP	17/ 4.3%	0	06 / 1.5 %	23

EMRR, multiple sclerosis recurring-remittent; EMSP, multiple sclerosis secondary progressive.

Table 3. Patients that migrated between the immunomodulators.

Clinical form	Interferon β 1a SC (n=121/%)	Interferon β 1a IM (n=6/%)	Interferon β 1b (n=63/%)	Glatiramer acetate (n=5/%)	Total (n=195)
EMRR	79/ 20.2%	06/ 1.5%	30 / 7.7%	05/ 1.3%	120
EMSP	42/ 10.7%	0	33 / 8.4%	0	75

EMRR, multiple sclerosis recurring-remittent; EMSP, multiple sclerosis secondary progressive.

Table 4. Demographic characteristics of patients that used the immunomodulators at the treatment start.

	EMRR (n= 163)	EMSP (n= 40)
Average - age	31.4	33.1
Male sex (%)	20.7	5.4
Female sex (%)	59.6	14.3
Time usage of the immunomodulators before discontinuing or migrating average (years)	2.6	2.0

EMRR, multiple sclerosis recurring-remittent; EMSP, multiple sclerosis secondary progressive.

Table 5. Reason survey for migration between the immunomod-ulators.

Reason for migration	n=120
Therapeutic error	4.6%
Progression	11.5%
Adverse reactions	15%
Pregnancy	13.8%
Abandon	18.4%
Not specified	36.7%

in 72 cases (18.6%). We observed that during this period 92 patients (23.6%) converted from type RRMS to SPMS, 195 (50%) migrated between immunological modulators and 108 (27.7%) used other associated drugs (immune supressive, immune globulins, symptomatic medicine).

In 157 patients (54%) of type RRMS, we achieve in verifying, the type of first outbreak of the patient, this being 25.5% sensitive and the optical neuritis with 22%. Initially in type RRMS 182 (62.5%) used interferon β 1a SC 3x/week, 15 (5.2%) interferon β 1a IM once a week, 85 (29%) interferon β 1b and 10 (3.3%) glatiramer acetate; type SPMS 63 (64.3%) used interferon β 1a SC, 4 (4.1%) interferon β 1a IM and

31 (31.4%) interferon β 1b. 35, (9%) patients stopped using medication, 19 (16.1%) migrated due to therapeutic progression failure of the illness and 18 (15%) due to adverse reactions, 305 (78.2%) patients completed 1 year of treatment and 66 (17%) completed 5 years treatment.

DISCUSSION

The criteria adopted by McDonald et al. were published in 2001, after the therapy start and so asto maintain the uniformity we used the Poser et al.[12,13]. The patients average that stopped using interferon in EMRR is 6 patients/per year, at EMSP it is 2.6 patients/per year and these values are less than those reported by the major multicenters. At the start accompaniment of these patients there was no glatiramer acetate available in Brazil (1997 to 2000); therefore some patients had to suspend interferon use because they had no alternative to use another medication[2], with the exception of judicial law access.

In Table 1 we presented 10 patients that started their treatment with glatiramer acetate, of these 5 patients migrated to another drug. As from 2001 free dispensation of glatiramer acetate started[2], after this we managed to start a survey related to this migration, 32 patients changed interferons to glatiramer acetate.

The average age was 35.2 years, 81.2% of the female sex and 18.8% male sex, 37.6% used interferon β 1b SC, 3.1% interferon β 1a IM and 59.3% interferon β 1a SC before they migrated to glatiramer acetate, 53% were EMRR and 47% EMSP. Related migration reason: 37.5% was due to a progression and 37.5% for therapeutic error, 12.5% for adverse reactions, 6.25 due pregnancy and in 6.25% the reason for the change was not specified.

The time elapsed to change medication was in average 3.5 years and the disease development time of these patients was average 3 years. We still have a short time period of glatiramer acetate use, so as to explain about the same. In relation to interferons β we did not have intention of comparing than so as

to demonstrate which the best was and the worst, but several studies and surveys demonstrate that in efficiency terms of medications all maintain the same average[5,8,11]. However, it is a fact that the drug risk failures occurs in the second year treatment, and could be due to the lack of patients response to the interferons β or to the emerging neutralizing antibodies[8].

The problem consists of one item as the majority of patients that use interferon β are not submitted to periodical antibodies mensuration (including this actual study/survey)[8]. Another question is the difficulty to know what is and how to determine therapeutic failure, even though being something subjective in science area[8]. We found certain difficulty to gather some retrospective information of these patients, attributable to medical team failure related to filling out of patients records.

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