Treatment of clinically isolated syndrome

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Introduction

Given that multiple sclerosis (MS) is an autoimmune disease whose first phase involves inflammatory processes with perivascular infiltration of lymphocytes and macrophages associated with demyelinization, immunomodulating drugs should be used for treatment. The action of these drugs is basically anti-inflammatory, and they are used to delay or stop the disease progression.

As explained in the previous articles, patients who at diagnosis undergo an isolated demyelinating process and have more than three lesions revealed through magnetic resonance imaging (MRI) are more likely to progress to clinically definite MS (CDMS) within 10 years [1]. Patients would benefit from early immunomodulating treatment, soon after its first clinical manifestations, delaying the disease progression and decreasing the degree of disability and the brain lesions typical.

Immunomodulating treatments

The medical and scientific community agree on a treatment for MS involving the suppression of autoimmune activity, which is responsible for damaging the central nervous system (CNS). However, the use of immunosuppressive agents has not proved successful, at least as expected.

In 1993, a study assessed the effect of corticosteroids on the conversion to MS in patients presenting clinically isolated syndrome (CIS). A total of 389 patients with acute optic neuritis without a diagnosis of CDMS were recruited for this trial. In it, patients were treated for 3 days with methylprednisolone at high doses (250 mg/6 h, i.v.) followed by prednisone for 11 days (1 mg/kg q.d.) and a 2-year follow-up. The results showed a significant reduction of risk for new clinical MS manifestations within the assessed period [2]. However, some years later another trial demonstrated that these corticosteroids were not effective over the 5-year follow-up, showing long-term inefficacy of this treatment [3].

Intravenous immunoglobulin (Ig i.v.), a nonconventional immunomodulating agent, has proved somewhat effective for treating patients with isolated demyelinating events. Patients at high risk of conversion to MS received Ig i.v. every 6 weeks for 12 months. The results showed that there was a reduction of 64% in the risk of CDMS as well as a significant decrease of the volume and number of T2 lesions [4]. However, the small number of participants (91 patients recruited) and the fact that all of them had been recruited and managed in one hospital only impair the consistency of the results. Including new centers and more patients to confirm the initial findings is needed.

Several phase III studies showed the benefit from immunomodulating treatment in patients with CIS (CHAMPS, ETOMS and BENEFIT, and PRECISE). Some of these studies are already published in their 3–5-year extension phases. Moreover, there is an ongoing phase III protocol to assess the effect of interferon (IFN)-1a s.c. (REFLEX). The results have not been published yet.

CHAMPS – CHAMPIONS studies

The first published clinical trial that achieved phase III included treatment with IFN β-1a i.m. in patients with a first, isolated demyelinating event. This clinical protocol was called CHAMPS (Controlled High-Risk Subjects Avonex Multiple Sclerosis Study). This protocol aimed at finding out if IFN β-1a i.m. (Avonex) had a beneficial effect on patients delaying the development of clinical confirmed MS by presenting with a new or worsening demyelinating event, including a 3-year follow-up [5]. The multicenter study recruited 383 patients (18–40 years old) who had a definite first acute demyelinating event (optic neuritis), incomplete transverse myelitis or brain stem and cerebellar syndrome, and at least two >3-mm T2 lesions in MRI, with one of them ovoid or periventricular. The onset of the visual or neurological symptom had to be less than 14 days before i.v. corticosteroid treatment (see further), which was

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not more than 27 days before entering the study. At incorporation in the protocol, patients received an initial 3-day treatment with prednisone (i.v.) and 11 additional days (oral). After this first treatment, patients received weekly i.m. IFN β-1a or were on placebo within 27 days after the first isolated demyelinating event. The primary endpoint was progression to CDMS, and the secondary endpoints were the changes in the MRI and the number of T2 and gadolinium-enhanced lesions. During the 3-year follow-up, it was demonstrated that the probability of CDMS decreased by 44% in the group with IFN β-1a compared with the placebo group. Considering data adjusted for age, type of initial event, extent of T2 lesions, and number of gadolinium-enhanced MRI lesions, the reduction was of 51%. Regarding brain lesions, the group on IFN β-1a had a great reduction in the extent of T2 lesions (91% compared with placebo group), less serious lesions, and a lower gadolinium-enhancing effect after 18 months. The treatment group had a mean increase of 1% in the number of T2 lesions versus 16% in the placebo group.

Analyses of CHAMPS subgroups

The subgroup analysis showed treatment effectiveness for the three clinical manifestations included in the protocol. Patients with optic neuritis had an adjusted rate of 42% of risk for CDMS, whereas those included in the protocol with transverse myelitis had an adjusted rate of 70% of conversion to CDMS; the adjusted rate of risk of CDMS for the brainstem and cerebellum syndrome groups was 60% [6]. Another study of the subgroup analyzed the benefit of treatment for those patients with a higher risk to develop CDMS. Patients who at inclusion in the protocol had more than nine T2 lesions in MRI, and more than one gadolinium-enhancing MRI lesion had their risk of a second demyelinating event reduced by 66%, showing that high-risk patients would benefit more from early treatment than the rest [7].

CHAMPS – extension phase

After finishing this clinical protocol, a 5-year, open-label extension phase started (CHAMPIONS). In this, patients were divided into two groups; the delayed-treatment (DT) group included patients who were part of the placebo group in CHAMPS, whereas the immediate treatment (IT) group had patients previously on IFN β-1a. Mean time from the first demyelinating event to the beginning of treatment was 30 months. The endpoints were the rate of development of CDMS (primary), the incidence of relapses, the degree of disability according to the Expanded Disability Status Scale (EDSS), and MR imaging [8]. The results of this trial showed that the DT group had 49% of probability of progression to CDMS, whereas the same risk in the IT group at 5 years was 37%. These data represent an adjusted rate of risk reduction of 43% compared with the control group. Although both treatment groups showed some beneficial effects from treatment with IFN β-1a, the DT group showed worse rates than those of the IT group, clearly demonstrating the benefit from delivering treatment to patients soon after the first isolated CIS events.

ETOMS study

The ETOMS study (Early Treatment of Multiple Sclerosis with Rebif) was another phase III clinical trial in which IFN β-1a (subcutaneous administration [s.c.]) was used. This was a multicenter, double-blind study with a 2-year follow-up in phase I. Its goal was to determine the efficacy and safety of IFN β-1a (Rebif) in delaying progression to CDMS in patients with clinically probable MS (CPMS) or laboratory probable MS (LPMS) according to Poser's criteria. In all, 308 patients with CIS and brainstem MRI suggestive of MS were recruited (18–40 years). These patients had more than four T2 lesions and the first event of neurological dysfunction within 3 months. They were classified as CIS unifocal or multifocal patients, depending on brain lesions (39% of the enrolled patients had multifocal lesions). The study primary endpoint was CDMS incidence (percentage of patients with a second relapse); the secondary endpoints were time to progression to CDMS, MRI T2 activity, changes in the volume of MRI lesions, and lastly, safety and tolerability of the drug. The treatment group received s.c. IFN 22 μg weekly. This trial showed that the weekly treatment with IFN resulted in a reduction of the adjusted rate of risk of CDMS of 35% at 2 years [9]. Regarding brain lesions, a significant reduction in the number of T2 lesions was observed compared with the placebo group (36% relative reduction).

As regards tolerability and safety of IFN β-1a, at the end of the study, 82% of treated patients had good results and only three patients (2%) had to withdraw from the study because of adverse events.

Of note is that the scheme and the administered doses during this trial were unsuccessful in previous treatments of relapsing–remitting patients with MS (RRMS). The efficacy from the same dose schedule in patients with a first clinical related event suggests once again the importance of early treatment in patients at risk of CDMS.

BENEFIT study

The BENEFIT study (Betaseron/Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment) was designed to assess the efficacy, safety, and tolerability of IFN β-1b in patients with a first event suggestive of MS in 2-year follow-up. BENEFIT was a multicenter, double-blind study that enrolled 468 patients presenting a first isolated demyelinating event (CIS) monofocal or multifocal with more than two T2 lesions in MRI indicating risk of MS. The treated group initiated treatment with betaferon/betaseron (8 million IU/250 μg) within 60 days after the first event. Opposite to the phase III studies mentioned above, this trial endpoint was the progression to CDMS according to Poser's and McDonald's criteria. In contrast to CHAMPS results, treatment with steroids was not homogenous and 70% of patients received corticosteroids in BENEFIT [10].

A great contribution from this study authors was the standardization of clinical criteria to define CIS presentation as monofocal or multifocal according to a minimum number of lesions that may explain the clinical presentation (signs and symptoms) [11]. As a consequence of this, patients who had been initially classified into monosymptomatic or polysymptomatic according to each physician's judgment were reclassified into monofocal or polyfocal according to these standardized criteria, which revealed a 16% of error in the original classification of the CIS type. BENEFIT results over 2 years showed a reduction of risk of CDMS of 50% according to Poser's criteria and of 46% according to McDonald's.

The analysis of the subgroup showed that early treatment in patients at low risk of CDMS was more effective than in the high-risk group, with more than nine gadolinium-enhanced multifocal lesions on MRI [10].

After this standardization by Uitdehaag, *et al*., the phase III CHAMPS study inclusion criteria by which patients were classified as monosymptomatic and polysymptomatic were re-evaluated. According to the new standardization, 30% of patients should have been considered multifocal. However, the risk assessment results using the new classification were not significantly different from those of the original study.

Although the criteria standardization and the centralization of data were crucial for a correct experimental design, the reclassification of completed trials' patients weakens the scientific value of the original conclusions and limits the analysis of results.

After BENEFIT was concluded, a 3-year extension was conducted. This new trial had an open-label design and a 6-month follow-up. As in CHAMPIONS, patients were divided into DT and IT groups. However, in this trial, there was an EDSS-confirmed progression in patients. The IT group had an EDSS-confirmed progression rate of 40% compared with DT group. It was also established that the required number of patients to be treated (NNT) to obtain benefit on one patient was 12 [12].

The extension phase showed a greater impact on IT patients treated on multifocal CIS with this measurement tool (EDSS for 6 months) compared with the original study, with more than nine lesions and gadolinium-enhanced lesions. However, the risk of progression to CDMS was reduced by 41% (37% in the IT group vs 51% with DT) and MS Functional Composite (MSFC) results were not significant (only PASAT [MSFC subtest] was $P < 0.05$).

This is the first report of an immunomodulating drug modifying the results of a cognition test in patients with CIS as from MS onset. If the main goal was to assess changes in EDSS, it would have been expected that the results of upper and lower limbs disability tests should have been significantly different. This inconsistency may originate in the very conception of EDSS, since in 0–3.5 ratings, the EDSS assesses neurological findings and not disability-related ones. Given that the patients' EDSS mean is 1, it may be concluded that EDSS is not a sound parameter for disability in these patients.

Even though these three phase III studies had different schemes and doses for each protocol and different enrollment criteria (Table 1), all treatment groups showed beneficial effects (Table 2). The assessment of the extension phases reveals that the DT groups never benefited as much as the IT groups.

PRECISE study

This phase III clinical protocol was introduced as "late-breaking news" in the American Academy of Neurology (AAN) 60th Annual Meeting held in Chicago in April 2008 [13]. This was a prospective, multicenter, double blind, placebo-controlled study in which 481 CIS patients with MRI results suggestive of monofocal MS (following Poser's criteria) were recruited. Copaxone 20 mg (s.c.) was administered q.d. versus the placebo group. The follow-up lasted for 36 months or up to the accomplishment of the endpoint: the conversion to CDMS. This clinical trial results showed that the risk of CDMS was reduced by 45% compared with placebo.

Approved treatments for CDMS at the regional level

The above-mentioned clinical protocols confirm the efficacy of immunomodulating treatments after a first demyelinating event in a patient at high risk of

Table 1 Summary of phase III studies including treatment with IFN-β

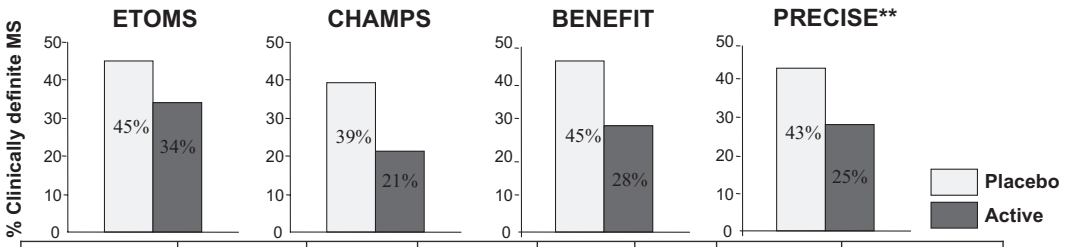
CHAMPS (2000)	ETOMS (2001)	BENEFIT (2006)
Weekly Avonex 30 µg i.m.	**Weekly Rebif 22 µg s.c.**	**Initially escalated Betaseron 250 µg s.c.**
Randomization 1:1	Randomization 1:1	Randomization 5:3
Age: 18–50 years	Age: 18–40 years	Age: 18–45 years
Withdraw from the study after the confirmation of CDMS	They can stay in the study as open label after confirmation of CDMS	They are offered active medication after the confirmation of CDMS
Optical neuritis and brainstem-cerebellum as first demyelinating event	First multifocal CIS with CNS compromise	CIS: first neurologic event with symptoms or signs of monofocal or multifocal with CNS compromise
27 days after recruitment	**90 days after recruitment**	**60 days after recruitment**
≥2 asymptomatic lesions, T2 lesions ≥3 mm, at least 1 p.v. or ovoid	**>T2 4 lesions or at least 3 T2 lesions if Gd +**	≥2 asymptomatic T2 lesions ≥3 mm, at least 1 p.v. or ovoid
Steroids within 14 days after the first event (100%)	Use of steroids without an agreed-upon regime (70%)	Use of steroids without an agreed-upon regimen (70%)

The main differences between the trials are highlighted.
CHAMPS, Controlled High-Risk Subjects Avonex Multiple Sclerosis Study; ETOMS, Early Treatment of Multiple Sclerosis with Rebif; BENEFIT, Betaseron/Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment; CDMS, clinically definite MS; CIS, clinically isolated syndrome; CNS, central nervous system.

CDMS and offer all treating physicians a therapeutic option for early treatment of MS. Nevertheless, the use of immunomodulating drugs is currently controversial – though clinical trials in patients with these symptoms have shown a delay in the progression to CDMS. No doubt that evidence from clinical trials represents a relevant source of information, but these data are usually taken from small numbers of patients in relatively short periods of time. Under these circumstances, general practitioners (GPs) have to decide everyday which patients would benefit from treatment, which drug they should use first, and what is the right time to start the therapy. The access to consensuses of clinical experts after their critical assessment of clinical trials might be useful for clinical professionals in making decisions under specific clinical circumstances. In Argentina, the first consensus on immunomodulating drugs for MS treatment was published in 2000 by the Argentine Society of Neurology Demyelinating Diseases Workgroup and the Argentine Multiple Sclerosis Consulting Medical Committee (in Spanish, EMA) [14,15].

The Argentine MS treatment guidelines published in 2006 include the recommendations from the 2000 consensus and some 2003 modifications together with new diagnostic criteria (McDonald's).

Table 2 Treatment of early MS data 2 years



	Placebo	IFN	Hazard ratio*	RR	ARR	NNT	Delay in days (Percentile)
ETOMS	45%	34%	0.65	35%	11%	10	320 (30%)
CHAMPS	39%	21%	0.45	55%	18%	6	412 (25%)**
BENEFIT	45%	28%	0.50	50%	17%	6	363 (25%)
PRECISE**	43%	25%	0.55	45%	18%	6	386 (25%)

ARR=absolute risk reduction; NNT=number needed to treat to prevent one patient converting to CDMS vs placebo over 2 years.
*Adjusted hazard ratio. ** upto 3 years ata
Comi G, et al. *Lancet.* 2001;357:1576-1582; Jacobs LD, et al. *N Engl J Med.* 2000;343:898-904; Kappos L, et al. *Neurology.* 2006;67:1242-1249; Kinkel RP, et al. Presented at the 22nd Congress of the ECTRIMS; September 29, 2006; Madrid, Spain. PRECISE press release Teva 2007

This document includes type A, B, and C recommendations for the treatment of CDMS patients in different progression phases. Among the most important recommendations, the consensus states that CDMS patients fulfilling Poser's and Mc Donald's criteria must immediately start treatment with immunomodulating agents, and furthermore, that these patients' access to agents with clear evidence of modifying the disease progression must be guaranteed. For patients with CIS (who are at high risk of Q2 CDMS is something clearly stated), clinical experts recommend to individually assess the kind of benefit that each patient could obtain from the treatment with IFN β-1a i.m., s.c., or with IFN β-1b [16]. An important point in these guidelines is that IFN-β must not be administered as a generic drug since each commercial product has different molecular structures, doses, and administration intervals. As recommendations supplementary to type A, the consensus guidelines state what immunosuppressive drugs such as mitoxantrone or cyclophosphamide may be used if the immunomodulating drug of choice fails or the disease manifestations continue.

However, not all countries have currently health policies that enable patients with first isolated events of the disease access to these treatments. The Brazilian health policies, for instance, do not authorize the prescription of IFN-β for CIS patients with high risk of CDMS. This restriction is closely related to the lack of an express recommendation in the Brazilian Committee for the Research and Treatment of Multiple Sclerosis and neuroimmunologic disorders (BCRTMS) consensus guidelines. Nevertheless, this consensus does mention the importance of MS early treatment [17]. Based on currently available data, these recommendations – first published in 2000 – stated very strict rules for the treatment with immunomodulating drugs, restricting its application to patients with MS defined by Poser's criteria (specifically, RRMS and Performance Scales for MS [PSMS]), and patients with a 6.5 or higher EDSS scoring. Furthermore, they recommended that treatment should be started with the minimum published doses and that there was no immunomodulating drug of choice – any drug could even substitute for any other one during treatment [18]. In 2002, a very detailed addendum to these guidelines was published [19–21]. These extended versions conduct a thorough review of the state-of-the-art treatments to update the original consensus – they particularly recommend individual treatment selection, educating patients about benefits and risks of their treatment, and highlight the need for monitoring adverse effects and patients signing an informed consent. Given the lack of scientific evidence recommending a particular drug, these extended consensus guidelines also recommend that the treating physician should consider the relative costs of drugs at treatment selection.

The Chilean consensus guidelines – not published yet – include recommendations for a comprehensive treatment of CDMS and CIS, including criteria for the research, diagnosis and treatment of these pathologies, and also considering the rehabilitation and symptomatic treatment of CDMS patients [22]. The main goals of this document are 1) to contribute to the current recommendations on these patients' management, based on the best scientific evidence available, expert consensus, and adapting to each country's context; and 2) to upgrade diagnosis and reduce the variability of the care and management of patients with MS.

The main class A recommendations in these guidelines promote a CDMS diagnosis based on McDonald's criteria, as well as a first-line treatment with IFN β-1b (250 μg on alternate days). If this drug is contraindicated, they recommend glatiramer acetate, azathriopine, mitoxantrone, or i.v. immunoglobulin, according to each physician. In confirmed cases of MS, the consensus recommends first-line treatment with IFN β-1b (160–250 μg, alternative days) or 1a (22–44 μg, three times per week). Another class A recommendation is to use methylprednisolone 1 g/day during 5 days in a patient with an acute outbreak of MS.

After a first demyelinating event (CIS), Chilean guidelines recommend IFN 1b (250 μg on alternate days) or 1a (22 or 30 μg once weekly) as first-line treatment. Also, in case of rehabilitation, the plan should be discussed with the patient, his family, or the person in charge according to the disease phase as well as follow-up.

Health and economic contexts of Latin American countries are similar in several aspects. So reaching a Latin American consensus for the treatment and management of patients with MS could help standardize the criteria for MS treatment and identify standards to measure the success of health policies.

Conclusions

The treatment of MS with immunomodulating drugs is promising, with IFN-β leading the therapeutic options. Analyzing clinical trials conducted on the different disease phases, there clearly is a therapeutic window for immunomodulating agents treating the first phases of MS (Figure 1). However, Q3 evidence of CIS and of a high risk of conversion to MS must be present before starting treatment so as not to cause adverse effects and not to expose the patient to unnecessary therapies, which would result in a loss of time and resources.

The treatment with IFN-β and glatiramer acetate reduced significantly the risk of CDMS in patients

who had a CIS. "Historic" comparisons among studies with different experimental designs, different enrollment criteria, and different endpoints must not be drawn; however, it is of note that the designs of the phase III studies described above applied different criteria for the use of steroids before starting treatment with a certain drug and for the time of intervention after the clinical event. Studies also confirmed that the higher the degree of initial activity of the disease, the higher the therapeutic efficacy. Regarding the therapeutic impact, it seems that the earlier the treatment, the higher the effect. Another aspect is that the effects of short-term treatments (2–3 years) may not predict long-term outcomes. According to the disease progression, the treatment of MS can last several years. So physicians must consider some factors such as long-term tolerance, degrees of treatment adherence, and the effect of neutralizing antibodies that often present much later than the follow-up period of a clinical trial.

Lastly, physicians must prepare patients to receive the prescribed treatment as well as information on the disease progression, available treatments, expectations, and possible adverse events, in order that the physician's decisions agree with the patient's wishes and be the best treatment option in each case.

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